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THE LONG-TERM IMPACT OF TREATMENT FOR INDIVIDUALS PRESENTING TO SPECIALIST SERVICES IN ENGLAND WITH OPIOID ADDICTION PROBLEMS

A thesis submitted for the degree of Doctor of Philosophy
at King's College London

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Between 2008 and 2012, when I was working with the then National Treatment Agency for Substance Misuse, we were enjoying a modicum of success from a series of papers published in *Addiction* and *The Lancet*. I had already seen what working in a psychopharmacology lab was like, but this felt different, this felt like I really belonged. Our papers had focused on the development of the Treatment Outcomes Profile and subsequent analysis of short-term change over the first six months of treatment. I thought I knew about regressions and transformations and analysis of variance, but working with Professor John Marsden was pure inspiration. I wanted more. If the relatively simple analysis of change between two time points could prove so exciting, what would it be like to delve into methodologies required for lots of extra time points? I will always be grateful to my colleagues at Public Health England for the opportunity to find out. Collectively, they provided the funding, data, software and time needed to get to this stage. I would like to specifically thank Kevin Shelton, Jonathan Knight, and Rosanna O'Connor.

This project would not have been possible without the support and guidance from Professor John Marsden and Professor Sir John Strang. They gave me space to find my own path and patience when so many attempts led to a dead end. John Marsden, in particular, has met with me countless times to discuss my latest whacky notion and how it might work and whether it would be useful. Looking back, the seeds he planted were always multilevel and not so latent after all. Thank you.

I am ever grateful to my wife, Lindsay, who throughout these seven years has been kind to me when I felt insecure and tough on me when I showed any signs of laziness. I would like to thank her father, Dr. Kenneth Chrystie, for taking an interest in my studies, even to the point of proof reading it. I would also mention my daughter, Freya, who effortlessly reminds me that it is important to laugh every day. Finally, I would like to thank my parents, Kathy and Bob, for encouraging me to follow my own star. Dad, I wish you were here to see where it led.

Abstract

Background

Opioid use disorder (OUD) is a debilitating, chronic psychiatric disorder. Opioid substitution treatment (OST) is associated with the suppression of illicit drug use, criminal offending and improved health. Efficacy trials estimate the response to short interventions and follow-ups but may not reflect outcomes from routinely delivered OST. National administrative databases circumvent this limitation. This thesis addresses the impact of publicly funded treatment for OUD using the English National Drug Treatment Monitoring System (NDTMS).

Aims

The thesis has three aims: to identify sub-populations of OUD patients at treatment admission and estimate their likelihood of completing treatment successfully over the next five years; to identify longitudinal sub-populations among those continuously enrolled in OST for five years based on heroin use and estimate their likelihood of completing treatment successfully; to identify longitudinal sub-populations based on alcohol and other drug use and estimate whether membership modifies the likelihood of completing treatment successfully.

Design and method

National, five-year, prospective, observational cohort studies of community specialist treatment for OUD by data linkage with NDTMS and fatal drug-related poisoning data from the Office for National Statistics. The population for Study 1 was adults who entered treatment between 1 April 2008 and 31 March 2009 (n=54,347). The cohort for Study 2 and Study 3 was a subset of Study 1 who were continuously enrolled in treatment for five years (n=7,719). An objective summative outcome measure was used, comprised of Successful Completion of treatment (clinician-verified) with No Re-presentation (SCNR) to treatment in the following six months. Analysis was by Latent

Class Analysis, Multilevel Latent Class Growth Analysis, Multinomial Logistic Regression and Multilevel Logistic Regression.

Findings

One fifth of discharged patients in Study 1 achieved remission from OUD. Of the four sub-populations of heroin users identified from their co-presenting substance use disorder at admission, heroin and crack cocaine users were less likely to recover. Those continuously in treatment for over two years were more likely to recover. Five longitudinal sub-populations (trajectories) of heroin users were identified for Study 2. Patients whose heroin use tended towards abstinence were more likely to recover in Year 6 and Year 7. Adjunctive psychosocial intervention during OST increased the likelihood of remission. Study 3 identified between three and five trajectory classes for crack cocaine, alcohol, cannabis and unspecified drug use. The continued high-level heroin use trajectory class during OST was associated with high-level crack cocaine and alcohol use and increasing unspecified drug use. Increasing use of crack cocaine was associated with a decreased likelihood that long-term OST was completed successfully.

Conclusions

This thesis presents the first national long-term evaluations of the impact of publicly funded treatment for OUD in England. As relapse requiring treatment is relatively common in the first six months following treatment completion, these studies highlight the importance of incorporating re-presentation to treatment in the assessment of remission. Sub-population analysis is an important facet in evaluating patients' progress through treatment, produces novel insights into the effectiveness of routinely delivered treatment and offers critical policy and clinical implications.

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Abbreviations used in this thesis

Abbreviation	Definition
95% CI	95% Confidence Interval
aBIC	Sample-size Adjusted Bayesian Information Criterion
aHR	Adjusted Hazard Ratio
AIC	Akaike Information Criterion
AOD	Alcohol and Other Drugs
AOR	Adjusted Odds Ratio
ATOS	Australian Treatment Outcome Study
BIC	Bayesian Information Criterion
BLRT	Bootstrapped Likelihood Ratio Test
BME	Black and Minority Ethnicities
DARP	Drug Abuse Reporting Program
DATOS	Drug Abuse Treatment Outcome Study
df	Degrees of Freedom
DORIS	Drug Outcome Research Study in Scotland
DRD	Drug-Related Deaths
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
GRoLTS	Guidelines for Reporting on Latent Trajectory Studies
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICC	Intra-Class Correlation
ICD	International Statistical Classification of Diseases and Related Health Problems
IMD	Indices of Multiple Deprivation
IQR	InterQuartile Range
IRD	Incidence Rate Difference
LCA	Latent Class Analysis
LCGA	Latent Class Growth Analysis
LSOA	Lower Super Output Area
MBC	Measurement-Based care
NDTMS	National Drug Treatment Monitoring System
NGO	Non-governmental organisation
NHS	National Health Service
NTORS	National Treatment Outcome Research Study
OMS	Outcomes Monitoring System
OR	Odds Ratio
OST	Opioid Substitution Treatment
ODU	Opioid Use Disorder

PBC	Performance-Based Contracting
PbR	Payment by Results
PHE	Public Health England
RCT	Randomised control trial
RDMD	Regional Drug Misuse Database
RECORD	The REporting of studies Conducted using Observational Routinely-collected health Data
RMC	Recovery Management Checkups
ROSIE	Research Outcome Study in Ireland
RRR	Relative Risk Ratio
SADQ	Severity of Alcohol Dependence Questionnaire
SBNT	Social Behaviour and Network Therapy
SCNR	Successful Completion and No Re-presentation
SD	Standard Deviation
SMR	Standardised Mortality Rate
STROBE	Strengthening the Reporting of OBservational studies in Epidemiology
SUD	Substance Use Disorder
TOP	Treatment Outcomes Profile
TOPS	Treatment Outcome Prospective Study
VLMR	Vuong-Lo-Mendell-Rubin
WHO	World Health Organisation

Chapter 1 INTRODUCTION

This thesis investigates the long-term effectiveness of treatment interventions for illicit drug addiction. The focus is on heroin, a powerful euphoric analgesic associated with high risk of morbidity and mortality. Data for the thesis comes from an England-wide administrative database from which a cohort is identified of approximately 50,000 people seeking treatment from specialist clinics in the National Health Service (NHS) and non-governmental organisations (NGO) for heroin addiction (formal diagnosis: opioid use disorder [OUD]). The thesis has an applied goal – to identify and characterise differential response to treatment to and inform clinical practice and policy on the treatment of drug addiction.

Throughout this thesis, I use the term ‘opiates’ to refer to heroin and all organic compounds which derive from the poppy plant. Opioids, on the other hand, refer to all drugs that act on the opioid receptor system in the brain, including synthetic drugs that bear little resemblance to the molecular structure of organic opiates. While OUD is a term that incorporates the misuse of all opioid drugs, this thesis is concerned only with individuals for whom heroin poses a significant problem. Throughout, the terms heroin, opiate and opioid are used synonymously unless otherwise stated. Further, the term OUD is utilised as the preferred terminology for those individuals accessing specialist addiction treatment services in England for heroin addiction problems.

The thesis is presented in six chapters. In **Chapter 1**, I provide a brief historical overview of the development of heroin as a medical problem in England and describe the nature and symptoms of OUD. Heroin (diamorphine) was discovered approximately 150 years ago. Since that time, when pharmaceutical diamorphine was largely confined to a small group of people prescribed the drug by a physician, problematic use of illicitly

manufactured heroin has increased to a widely recognised problem exerting a significant effect on contemporary society. Over time, the national strategic response has also shifted: penal and medical policies have been implemented and adapted; information systems providing critical evidence on the effectiveness of treatment have been established and disestablished; and funding and policy support for treatment has waxed and waned. Today, one of the most significant public health indicators of the heroin epidemic – fatal overdose – is at an all-time high.

Large scale treatment effectiveness studies consistently demonstrate that exposure to treatment interventions is associated with suppression in the use of heroin, a reduction in the cost to society in terms of criminal offending and criminal justice-related costs, and a reduction in the risk of death and the transmission of blood-borne viruses. These studies are, however, expensive, time consuming, necessarily formed of only a sample of those affected and are not designed to capture change in the context of ongoing, continuous, treatment. National administrative databases circumvent these limitations, and provide near real-time performance management reports to treatment services, treatment commissioners and those public bodies responsible for overseeing the delivery and effectiveness of treatment.

In **Chapter 2**, I provide an overview of the methodologies employed in three interconnected analyses for the thesis – each published in a scientific journal during the course of my studies for a PhD. Taken together, these studies shine light on the effectiveness of treatment for OUD over five-years. Follow-up studies over this time frame are rare in addiction science. Using latent cross-sectional and longitudinal statistical procedures, I identify sub-groups of heroin users at the start of treatment and over time while enrolled in treatment.

In Study 1, reported in **Chapter 3**, I selected all individuals accessing treatment for OUD in England in 2008/09 and followed them over a five-year period (until the end of 2013/14). Heroin users presenting to treatment are far from homogenous, and four sub-populations are identified according to the concurrent problematic psychoactive substances with which they present to treatment using Latent Class Analysis (LCA). I introduce an objective summative (proxy) measure of treatment effectiveness (i.e. the successful completion with no re-presentation to treatment within six months). From this analysis, I demonstrate that presenting to treatment with concurrent cocaine (a powerful, addictive stimulant) is negatively associated with the likelihood of recovery from OUD.

In **Chapter 4**, I present Study 2, which contains a detailed assessment of those patients who had been continuously enrolled in opioid substitution treatment (OST; with oral liquid methadone or sublingual tablet buprenorphine) for the five-year period. Sub-populations are identified based on their relative longitudinal response to treatment. Using Latent Class Growth Analysis (LCGA), I show that patients whose heroin use trajectory places them on a course towards abstinence are those most likely to be found to have overcome OUD in the subsequent Year 6 and Year 7 phase of follow-up.

Study 3 is reported in **Chapter 5**. Here, I again use LCGA to model the frequency of use of other drugs and alcohol during heroin treatment. By examining the relationship between heroin and other drug and alcohol change trajectories, I demonstrate that those patients who make the least improvement in terms of heroin are generally those clients for whom crack cocaine is also a persistently used substance.

Chapter 6 explores the clinical and policy implications of the three studies presented in this thesis. It integrates the findings within the wider literature and sets out the

implications of these findings for the ongoing utilisation and development of the English National Drug Treatment Monitoring System (NDTMS). The strengths and limitations of the studies are reviewed and limitations of the national monitoring system are considered. Chapter 6 concludes with the next immediate research question using the cohort described throughout this thesis.

1.1 HEROIN

1.1.1 A BRIEF HISTORY OF HEROIN

Heroin is a derivative of the poppy plant *Papaver somniferum*, and was first synthesised almost 150 years ago in the United Kingdom (Wright, 1874). Heroin was not the first drug to come from this plant. Opium had been used for centuries by this point, and morphine was isolated from the poppy extract in 1805 (Krishnamurti and Rao, 2016). Diacetylmorphine, as it was then known, was later synthesised by simple acetylation of morphine at St. Mary's, London, in 1874. This innovation went largely unnoticed until it was rediscovered twenty years later, apparently independently, at which point the seeds of the modern-day epidemic were planted. In 1898, the German pharmaceutical company, Bayer & Company, marketed the drug as a cough suppressant and it was used in medicine in many countries around the world. The name 'heroin' was coined by Bayer & Co., and alludes to an ancient Greek hero honoured on account of his deeds (Sneader, 1998).

The addictive liability of heroin was not recognised in the early years of availability. It was proactively advertised in medical journals as preferential to morphine as it was not habit forming (Phillips, 1912). Nonetheless, the non-therapeutic – or illicit use – of heroin soon emerged. Heroin pills could be crushed and sniffed into the nose, much like snuff tobacco, and reports of smoking heroin pills began to emerge from Shanghai in the 1920s (Phillips, 1912; Strang et al., 1997a). The smoking of pills involved gently

heating a pill inserted into a hole drilled into a porcelain vase and smoking the fumes through a bamboo tube. This process was later refined in Hong Kong during the 1950s into a technique that came to be known as 'chasing the dragon'. This new technique involved heating heroin powder over tin foil and inhaling the sublimated vapours. Chasing the dragon quickly spread out from Hong Kong. Its use was noted in Thailand in the 1960s; then in Singapore, Burma, Malaysia and the Netherlands in the 1970s; and in India and the UK in the 1980s, and Switzerland and Spain in the 1990s (Strang et al., 1997a).

While addiction to morphine and heroin was a recognised problem in England during the 1920s, the prevalence of the problem was considered rare and diminishing (Berridge, 1980; Rolleston, 1926). The first epidemic of illicit heroin use in England appears to have begun in London in the early 1960s, at a time when virtually all available heroin came in the form of pharmaceutical tablets (Strang et al., 1997b). By 1966 it had spread beyond London (James, 1969). This was England's first heroin 'epidemic' – 'epidemic' in the sense that the heroin habit (a learned behaviour) was spread by users to friends and acquaintances (Reuter and Stevens, 2008). One patient, for example, was reported to have introduced 11 other people to heroin addiction (Chapple and Marks, 1965). The increase in heroin addiction during the 1960s coincided with an arrival of 'fifty' (James, 1969) or 'hundreds' (Strang et al., 1993) of injecting addicts from the United States (US) and Canada seeking to capitalise on England's propensity to prescribe heroin to addicts and growth of an injecting subculture in London emerged. It was thought at the time that the rise in the number of new addicts was due in large part to doctors prescribing heroin in greater amounts than required by patients, enabling patients to sell the surplus (Edwards, 1969; Patricia, 1965). The profile of users also changed during the 1960s. No longer were they middle-aged and older, who had developed the condition through prescribing for

legitimate medical problems, they were younger people who had acquired their addiction through illicit means. The ratio of therapeutic to illicit acquisition of addiction had altered substantially, from 5:1 to 1:4 (James, 1969).

There were two further epidemics in England during the first half of the 1980s and the first half of the 1990s (Strang and Taylor, 1997). The epidemic of the 1980s was probably influenced by the increased imports of illicit heroin from South East Asia in the early 1970s and from South West Asia in the late 1970s (Strang et al., 1997b). The difference between the decades is stark. In 1989 heroin was concentrated in the North West of England, East of England and in London, but by 1997 the majority of the country had witnessed new outbreaks (Parker et al., 1998).

England was not alone among the countries of Great Britain in experiencing a rapid onset of heroin addiction within its population. There were what were considered minor waves of heroin use in Glasgow (Scotland) in 1967, 1971 and 1976, but the major shift occurred between 1980 and 1981 when referrals to the two available drug clients increased by more than 500% to 174 individuals (Ditton and Speirits, 1982). By 1984, almost 300 Scots were being treated for opioid addiction (Drummond, 1986). Heroin is now recognised as the most harmful type of drug in health terms, and there are now an estimated 17.7 million users worldwide (United Nations Office on Drugs and Crime, 2017).

1.1.2 OPIOID USE DISORDER

Heroin addiction is a debilitating and often chronic bio-behavioural disorder. It is contemporaneously diagnosed as opioid use disorder (OUD, herein) in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association, 2013), or opioid dependence under

the World Health Organization's International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10; World Health Organization, 2016).

OD is characterised by a set of cognitive, behavioural and physiological symptoms, and chronic consumption of heroin is usually accompanied by several negative consequences. One of the earliest definitions described a heroin addict as "[a] person who, not requiring the continued use of a drug for the relief of the symptoms of organic disease, has acquired, as a result of repeated administration, an overpowering desire for its continuance, and in whom withdrawal of the drug leads to definite symptoms of mental or physical distress or disorder" (Rolleston, 1926, p392).

Both the nosology (i.e. how a disorder is classified) and the nomenclature (i.e. how a disorder is named) of addiction has changed markedly in the 60 years since DSM-1 was first published in 1952 (Nathan et al., 2016; Robinson and Adinoff, 2016). The first DSM used the term 'drug addiction' and categorised it under sociopathic personality disorder (American Psychiatric Association, 1952). Sixteen years later, DSM-II applied the term 'drug dependence' and shifted the categorisation to that of 'personality disorder and certain other non-psychotic mental disorders' (American Psychiatric Association, 1968). From DSM-III to DSM-5, the disorder was classified independently although the name given to it changed from 'substance use disorders' (American Psychiatric Association, 1980) to 'psychoactive substance use disorders' (American Psychiatric Association, 1987) to 'substance-related disorders' (American Psychiatric Association, 1994) and, finally, to its current form of 'substance-related and addictive disorders' (American Psychiatric Association, 2013).

DSM-III drew a distinction between opioid abuse and opioid dependence, and this terminology continued through DSM-IV. Just as the term 'addiction', however, was

supplanted with the term ‘dependence’, the latest version of the manual (DSM-5) has now adopted to the term ‘opioid use disorder’ (OUD). In doing so, the DSM system has removed the concept of heroin ‘abuse’. OUD is now conceptualised as falling on a severity continuum, ranging from mild, when two or three criteria are met to moderate (four or five criteria) and severe (six or more criteria) (see **Table 1.1**).

Table 1.1 Diagnostic criteria for opioid use disorder (DSM-5)

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfil major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
b. A markedly diminished effect with continued use of the same amount of an opioid.
11. Withdrawal, as manifested by either of the following:
a. The characteristic opioid withdrawal syndrome
b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

Similar evolutionary changes can be seen in the ICD (Aggarwal et al., 2008; Maddux and Desmon, 2000; Saunders, 2006). It was not until publication of the seventh edition of the ICD, ICD-7, in 1967 that substance-related problems were incorporated into this classification system (World Health Organization, 1967). The current edition, the ICD-10, was first published in 1992 and subject to several iterations (World Health Organization, 1992; 2016) and uses the term harmful use for those whose opioid use is causing damage to their physical or mental health. The term opioid dependence is applied to those individuals with at least three symptoms present of those listed in

Table 1.2.

Table 1.2 Diagnostic criteria for opioid dependence (ICD-10)

(a) a strong desire or sense of compulsion to take the substance;
(b) difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use;
(c) a physiological withdrawal state when substance use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;
(d) evidence of tolerance, such that increased doses of the psychoactive substances are required in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol- and opiate-dependent individuals who may take daily doses sufficient to incapacitate or kill non-tolerant users);
(e) progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects;
(f) persisting with substance use despite clear evidence of overtly harmful consequences

1.1.3 THE LIFE COURSE OF OPIOID USE

The life-course epidemiology of heroin use has been described by Darke (2011). There is a logic sequence of events in the development of OUD: a person must first be exposed to the opportunity to take the drug and, subsequently, the person must actually use the drug, and then take it repeatedly. In the case of opioids, it has been estimated that around 5% of the population are exposed to the opportunity to consume heroin, with males having greater exposure than females (7.8% versus 3.2%; Van Etten and Anthony, 1999). The same study indicated that around 20% of those exposed subsequently took the drug, with males and females having the same propensity to do so.

Simply using the drug, however, does not inevitably lead to the development of OUD. It has been reported that around one quarter of opioid users will develop OUD in their lifetime (Anthony et al., 1994; Ashton, 2002; Degenhardt and Hall, 2012; Gable, 1993). This indicates that opioids confer the greatest dependence liability of all psychoactive substances – second only to nicotine. Initiating heroin use at an early age (before 21 years), appears to be strongly associated with a more rapid progression to regular use, a longer lifetime duration of heroin use and more negative drug-related health and social consequences (Woodcock et al., 2015).

Once established, OUD typically follows a chronic course, causing substantial health, social and economic problems. OUD is now the single largest contributor to the global burden of disease attributable to illicit drug use (Degenhardt et al., 2013). Over a 30 year period, between 20% and 25% of heroin users will not demonstrate any appreciable decrease in consumption (Grella and Lovinger, 2011; Hser et al., 2001). They are likely to suffer extensive and worsening physical health and mental health

issues and – due to the illicit nature of heroin distribution and personal cost of addiction – some people also have involvement with the criminal justice system (Darke, 2011).

1.1.4 NEUROBIOLOGY OF HEROIN

The primary receptors in the brain involved in the reinforcing and rewarding properties of opioids are the mu opioid receptors, although opioids also have an affinity to delta and kappa receptors (Negus et al., 1993). Once the opioid is linked with the mu receptor, it activates the reward circuitry of the brain, the mesolimbic dopamine system. The ventral tegmental area in the mesolimbic system triggers the release of dopamine in the nucleus accumbens, generating feeling of pleasure, and appears to be the primary motivating reason for chronic opioid use (Kosten and George, 2002). In time, the release of dopamine in response to the continued administration of opioids is attenuated. A number of mechanisms for receptor attenuation have advanced, including: down-regulation (a reduction in the number of receptors); desensitisation (a reduced receptor response); phosphorylation (the chemical addition of phosphoryl to receptors), and endocytosis (internalising material from outside the receptor)(Allouche et al., 2014). As OUD develops, a desired 'high' becomes harder to achieve due to tolerance while at the same time the 'low' or 'come down' becomes more unpleasant, adding a further motivation for continued drug taking – alleviation of negative withdrawal symptoms.

The consequences of this attenuation are twofold: the person is likely to need greater quantities of the drug to achieve the same effect and the brain's reward system no longer activates (or is under-activated) in the presence of previously rewarding activities (Volkow et al., 2016). The latter of these may be the reason many individuals with OUD no longer engage in important social, occupational or recreational activities, one of the defining features of the disorder (American Psychiatric Association, 2013).

To place the impact of tolerance in context, the administration of 10mg of pharmaceutical diamorphine may induce respiratory failure in persons unaccustomed to the drug, but one patient with OUD was observed to self-administer 1,140mg of pharmaceutical diamorphine in 24-hours (Stimson and Oppenheimer, 1982).

Another consequence of repeated stimulation of the dopaminergic pathway is that adaptations occur in the amygdala and forebrain structures. These changes induce negative emotions – such as dysphoria, anxiety and irritability – and particularly when drug supply is no longer available. The person's negative reactivity to stressful situations also increase (Volkow et al., 2016).

In the absence of opioids, people with OUD experience a set of physical withdrawal symptoms, including diarrhoea, sweats, chills, dilated pupils, nausea, vomiting, and increased heart rate or blood pressure – described as a subjectively severe but objectively mild set of symptoms (Farrell, 1994). Neurologically, these symptoms are associated with a surge of noradrenergic activity in the locus coeruleus. The locus coeruleus is a noradrenergic centre in the brain. It is also the anatomical intersection of opioid and stress signalling (Scavone et al., 2013). Alpha-2 adrenergic receptor agonists such as clonidine and lofexidine can be prescribed to regulate this hyperactivity (Gossop, 1988; Strang et al., 1999), with the latter associated with fewer side effects.

1.1.5 THE EMERGENCE OF CRACK COCAINE

Cocaine hydrochloride (usually referred to as powder cocaine) is usually snorted, but it can also be mixed with water and injected. This form of cocaine cannot be smoked as the salt is destroyed by heating (Cornish and O'Brien, 1996). 'Crack' cocaine is a colloquial name for a base form of cocaine hydrochloride that can be smoked. There

are two methods for creating crack cocaine from powder cocaine, the simpler of which involves combining it with sodium bicarbonate and heating until a solid is formed (Cornish and O'Brien, 1996).

The development of crack cocaine is unclear and may have emerged by accident. As outlined by Streatfeild (2002), at some point during the 1970s an American trafficker became aware that Peruvian growers of cocaine were smoking a sulphate form they called 'basé' (a name which had nothing to do with the chemical itself). Nonetheless, this trafficker may have had contacts in the chemistry world and realised that cocaine could be separated from the hydrochloride by adding a strong alkali and creating cocaine crystals. The result was quite different from than the crude cocaine sulphate the Peruvians were smoking. It was still technically the same drug, but it was much refined. For those used to snorting cocaine powder, with only the relatively small surface area of the nasal cavity to cross slowly into the bloodstream, the combined surface area of both lungs were now available resulting in a very fast and powerful 'hit'.

The first outbreak of a crack cocaine epidemic was probably in the Bahamas in 1979 (Streatfeild, 2002) and by the late 1980s crack cocaine began to emerge in the US where it was quickly seen as a major risk to public health (Minyard, 1986; Thomas, 1989; Washton et al., 1986). There were significant concerns that cocaine would have an immediate and significant impact on the health of the UK population. Cocaine was declared to be "the most serious peace-time threat to our national wellbeing" (House of Commons, 1985 cited in Strang et al., 1990). The potential for crack cocaine to be readily subsumed into the lifestyle of a heroin addicts seems obvious in retrospect. In 1886 the phenomenon of 'cocomania', the combined addiction to cocaine and morphine, had been described by Erlenmeyer (James, 1969). The modern day

equivalent, 'speedballing', involves the simultaneous exposure to both crack cocaine and heroin (Leri et al., 2003a).

Early reports from treatment services in England showed that the prevalence of cocaine use among people addicted to heroin rose from 13% to 29% between 1987 and 1989. Detailed examination of those reporting past-month cocaine use showed, however, that crack cocaine rose from 15% to 75% over the same period, and of those reporting cocaine use, 95% were consuming it alongside heroin (Strang et al., 1990). In a sample of 500 opioid injectors in London, most of whom were recruited from the community as opposed to treatment services, the use of crack cocaine rose from 1% in 1990 to 27% in 1993 (Hunter et al., 1995). Latest statistics from England report that more than half (54%) of patients who entered treatment in 2017/18 for OUD also reported a concurrent crack cocaine problem (Public Health England, 2018a).

There is wide recognition that crack cocaine is a substantial public health problem. Crack cocaine accelerates the progression of HIV/AIDS (Baum et al., 2009) and is associated with high criminal involvement (Pierce et al., 2015b). Cocaine is also associated with reduced effectiveness of treatment for OUD in that the frequency of heroin use is substantially higher in those who also use cocaine (Hartel et al., 1995; Heidebrecht et al., 2018; Marsden et al., 2009).

1.1.6 THE MEDICO-LEGAL RESPONSE

Restrictions on the availability of 'hard' drugs had already been imposed by the time heroin was first synthesised. The first attempt to control 'the sale of poisonous drugs' in Britain came in the form of the Poisons Bill in 1819, which failed to become law (Stimson and Oppenheimer, 1982). It was only with the passing of the Arsenic Act in 1851 that some form of regulation began to emerge. The Arsenic Act also positioned

the Pharmaceutical Society of Great Britain to successfully lobby for further restrictions on those eligible to sell (and make money from) drugs. Prior to the introduction of the Pharmacy Act in 1868, when certain drugs were restricted to being dispensed by pharmacies, opium was readily available in apothecaries, herbalists and retail shops (Berridge, 1982). Between 1868 and 1920, an addict could still obtain opium from a pharmacy without prescription (Merry, 1975). It was only with the passing of the Defence of the Realm Act in 1916, specifically regulation 40B generally referred to as DORA 40B, that a doctor's prescription was required by law for the acquisition of certain substances, mostly notably cocaine.

The Dangerous Drugs Act was introduced in 1920 to meet Britain's obligations under the 1912 International Opium Convention at The Hague, obligations which were further reinforced under Article 295 of the Treaty of Versailles in 1919 (Ashton, 2002). Followed by the Dangerous Drugs and Poisons Acts of 1923, 1925 and 1928, the manufacture, sale, possession, import and export were criminalised, although allowances were made for legitimate use. The penal emphasis and police search powers were also increased during the 1920s.

At the same time, the Dangerous Drugs Act allowed medical practitioners to prescribe heroin for legitimate reasons. Contemporary legitimate uses include the treatment of myocardial infarction, palliative care, pulmonary oedema and post-operative pain (Gossop et al., 2005a). The Rolleston Report of 1926 reaffirmed doctors' rights to prescribe heroin to persons addicted, even while acknowledging that heroin addiction was rare in Britain at the time. The report was clear that heroin addiction "should be regarded as a manifestation of a morbid state, and not as a mere form of vicious indulgence" and that it would be legitimate to prescribe heroin to "...those who are undergoing treatment for cure of the addiction by the gradual withdrawal method; and

persons for whom, after every effort has been made for the cure of the addiction, the drug cannot be completely withdrawn..." (Rolleston, 1926, p392-393). This unique approach, which is to say an approach with a legitimate medical structure within a penal framework, became known as the 'British system'.

In 1958, after press reports of a new form of heroin use by young people, the Ministry of Health convened the Interdepartmental Committee on Drug Addiction. Headed by Sir Russell Brain, the 'Brain Committee' first reported in 1961 and effectively concluded that there was no real increase in drug use in Britain at the time (Interdepartmental Committee on Drug Addiction, 1961). It did not take long for this optimistic view of events to be superseded. Thirty-five years had passed between the Rolleston Report and the report from the First Brain Committee, yet a second review was convened only three years following the publication of the latter, again headed by Sir Russell Brain. This time round, a significant increase in the heroin using population was noted, alongside recommendations to tackle the growing problem (Interdepartmental Committee on Drug Addiction, 1965).

Dedicated treatment centres, known as 'Clinics', started to open from April 1968 onwards (Stimson and Oppenheimer, 1982) and by the autumn of that year there were 39 Clinics providing treatment. By October 1968, there was a total of 904 patients accessing these Clinics. Alongside the opening of the new Clinics in 1968, the Dangerous Drugs (Supply to Addicts) Regulations came into force across the country. One of the aims of the British system was to prevent patients from accessing heroin on the black market. These regulations, however, stipulated that doctors should be certain a patient arriving at the clinic was indeed an addict and that the amount of heroin prescribed should be conservative. As pointed out at the time, however, these intentions were beset by unexpected consequences: an addict refused a prescription,

or prescribed too little, would be motivated to seek out supply on the black market (Edwards, 1969). Indeed, by the end of the 1960s, the black market for heroin was flourishing in Britain, although it should be noted that this was an illicit market in pharmaceutical diamorphine and not an illicit market of the illicitly-manufactured heroin of today (Stimson, 1987).

It only became apparent in 1986 that injecting drug users were at a particular risk of contracting and transmitting HIV through the sharing of injecting equipment (Robertson et al., 1986). The United Kingdom was not alone in this as many countries in Europe and beyond had particularly high prevalence rates of HIV in the injecting drug user population during the 1980s (Hamers et al., 1997). An influential report at the time by the Advisory Council on the Misuse of Drugs noted that 'HIV is a greater threat to public and individual health than drug misuse' (Advisory Council on the Misuse of Drugs, 1988). This report prompted a national strategic focus on preventing injecting drug users from acquiring and transmitting the virus. What is important to note is that abstinence from opioid use was not the only recognised means of achieving these goals; risk reduction strategies were also promoted for those who could not achieve abstinence. Needle and syringe provision became widespread as funding allocated to this preventive measure escalated from around £1.3million in 1987/88 to £16.1million in 1993/94 (Stimson, 1995). Crucially, a greater clarity around the purpose of changing injecting behaviour among treatment providers was brought to the fore (Strang, 1998). Clinicians could target intermediary steps away from high-risk behaviours such that, for example, cessation of sharing equipment could precede cessation of injecting entirely. The strategy was effective, at least until recently when there a rapid re-emergence of HIV among injecting drug users was reported in Glasgow: HIV rates in this population, usually very low, increased from 0.1% in 2011 to 4.9% in 2018 (McAuley et al., 2019). While this is still in the estimated range of HIV prevalence in the injecting population in

Western Europe (3.2-6.0%), it is higher than Australasia (0.8-1.4%) and much lower than the global estimate of 10.8-24.8% (Degenhardt et al., 2017).

1.1.7 INFORMATION SYSTEMS IN ENGLAND

Accurately capturing the extent of the heroin addiction population is crucial to the formulation of a strategic response. By far the easiest approach is to simply tally the numbers of unique patients coming into contact with treatment centres. Initial efforts began in the 1930s and since then there has been a general shift from informal methods of capturing this information towards more formal and, latterly, computerised methods. A mandatory obligation was placed on all doctors from 1968 onwards to record and to notify the 'Addicts Index' (see below) when they treated or otherwise attended a heroin addict. The late 1980s and early 1990s saw the introduction of computerised information gathering systems in each region of Great Britain. With the dawn of the new millennium, the English regional systems were integrated into a national drug treatment monitoring system.

1.1.7.1 HOME OFFICE ADDICTS INDEX

From around 1935 there was an informal arrangement to notify the Home Office of persons addicted (Corkery, 2002). The number of addicts known to the Home Office was relatively small, reinforcing Rolleston's statement that addiction was rare at this time. There were around 700 known addicts in 1935 and there was a general decline until 1953 when only 290 people were recorded on the index (Stimson and Oppenheimer, 1982). Relatively small increases followed in the following years and in 1960 there was a total of 437 people on the index. Rapid increases were witnessed in the mid-1960s and by 1968 there were 2,782 recorded addicts.

It is interesting to note that the rise in the 1960s seems almost entirely due to changes in the recording of males on the index. In 1936, when gender could be disaggregated,

there were 313 males and 300 females on the index. By 1968, there were 2,161 males and 621 females, indicating that while the population of known females doubled in this period, the male addict population had increased seven-fold (**Figure 1.1**).

The recording of heroin, specifically, on the index did not emerge until 1954 when only 57 (18%) of those on the index were so recorded (**Figure 1.2**). This had changed substantially by 1968, when 2,240 (81%) of those on the index were notified as 'heroin addicts'. This dramatic increase was the background to the 1968 Dangerous Drugs (Notification of Addicts) Regulations. From 1968, doctors prescribing heroin had to be specially licenced by the Home Secretary, the licence was only valid at a named hospital, and doctors had a statutory duty to report patients to the Home Office Addicts Index. The notification of addicts to the Home Office was entirely straightforward. For some General Practitioners, for example, re-notifying the index about a particular individual each year was prone to under-reporting and the clarity (or interpretation) of the addiction diagnosis could lead to discrepancies between those being treatment and those being notified (Robertson and Bucknall, 1985). Nonetheless, the number of individuals recorded on the index kept accelerating and by 1996, the year before the index was closed, there were 43,372 individuals on the system, 30,573 (70%) of whom were addicted to heroin (Morgan, 2014).

The Addicts Index was not without its critics. There was an apparent lack of investment in analysis of the data and the shifting profile of users was only noticed in retrospect, leading the authors to conclude that "...our new data-collecting power now needs to be accompanied by at least some investment in time for academic study of these collected data, so that information may be translated into knowledge and so that science may better serve the policy-making process" (Strang and Taylor, 1997, p47).

1.1.7.2 REGIONAL DRUG MISUSE DATABASE

Regional Drug Misuse Databases (RDMD) were set up in England, Wales and Scotland in 1990 to monitor the demand for treatment (Donmall, 1999). These overlapped with the Home Office Addicts Index until the index was closed in 1997, although doctors were still expected to continue to report anonymous data to the RDMD (Tregoning, 1998). The rationale behind this decision was that the Home Office Addicts Index did not provide a comprehensive picture of addicts accessing treatment. It only captured those individuals being treated by doctors with the result that non-medical treatments were not captured. It also did not capture individuals who were addicted to certain substances, such as amphetamines and benzodiazepines, which doctors were not required to notify (Government Statistical Service, 1994).

Statistics from the RDMD were published by the Department of Health, and cover the six-month period ending 31st March or 30th September from 1993 to 2001. Between March 1993 and March 2001, the number of individuals accessing treatment increased 86%, from 17,822 to 33,200 (**Figure 1.3**). Throughout the same period, the proportion of individuals reporting heroin as their primary drug increased from 47% to 67%. It is interesting to note given the arguments given for closing down the Addicts Index – specifically with regards the idea that the index did not provide comprehensive reporting of all addicts being treatment – that data from the RDMD on 31 March 1996 point to 23,313 individuals being in receipt of treatment compared with the 43,372 recorded on the index.

1.1.7.3 NATIONAL DRUG TREATMENT MONITORING SYSTEM

The RDMD was replaced by the National Drug Treatment Monitoring System (NDTMS) in 2001 when the National Treatment Agency for Substance Misuse was formed and took charge of treatment in England. Comprehensive reporting from the NDTMS was not, however, available until 2005/06. As can be seen in **Figure 1.4**, the first year

reported 216,802 individuals accessing treatment in that year, 65% of whom were treated for opiates. In the latest year of reporting (2017/18), there were 268,390 individuals accessing treatment, 53% (n=141,189) of whom were being treated for opiates (Public Health England, 2018a).

1.1.8 PREVALENCE ESTIMATES

A more difficult task than counting those accessing treatment services is to estimate the total population of persons with OUD in the country. The prevalence of OUD in the general population aged 15-64 have been estimated several times in England, starting in 2004/05 (**Figure 1.5**). As can be seen, the estimates of the number of opioid users have shown a decline from a peak of 286,566 (95% Confidence Interval [CI] 281,668-299,394) in 2005/06 to 261,294 (95% CI 259,018-271,403) in 2016/17 (Hay et al., 2019). By cross-referencing these estimates with the number of individuals accessing treatment, it has been concluded that 49% of the OUD population in England accessed treatment in 2005/06, and this proportion increased to 56% at the time of the latest prevalence estimates in 2016/17.

To put these prevalence estimates in context, it is useful to look at the rate of individuals with OUD per 1000 population. In the US, it is estimated that 2.6 people per 1,000 aged 12 and above used heroin in the past year (Jones et al., 2015). In Europe, the estimated annual heroin use prevalence is 4 per 1,000 aged 15-64 and this ranges between 1 and 8 per 1,000 (EMCDDA, 2016). In England, the current estimates 7.4 per 1,000 among people aged 15-64 in England (Hay et al., 2017), making the rate in England one of the highest of Western countries. There is wide regional variation in the rate of opioid users per 1,000 population within England. In the northern parts of the country (**Figure 1.6**), the prevalence rate is almost twice that of the South East region.

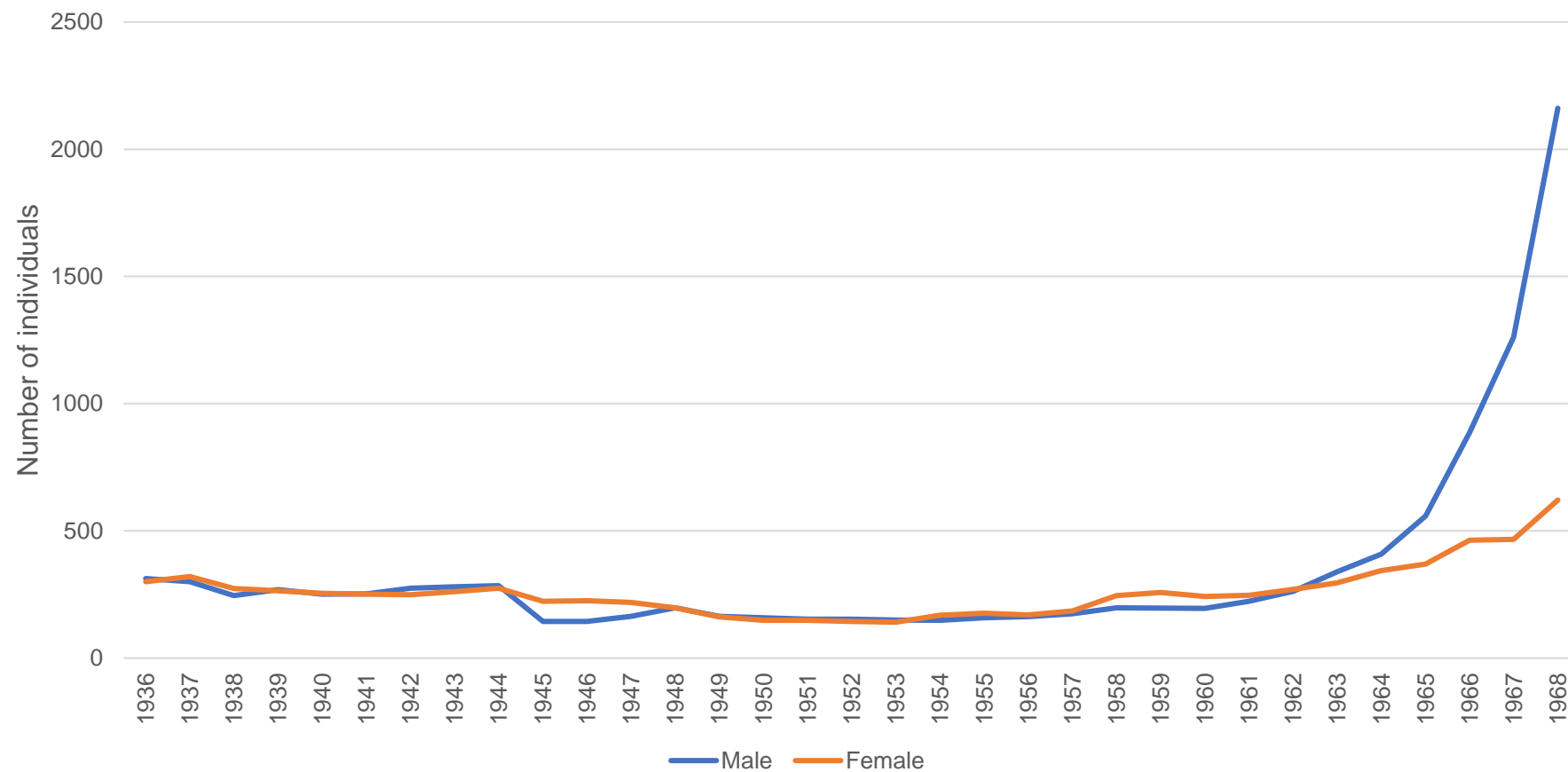


Figure 1.1 The number of males and females recorded on the Home Office Addicts Index, 1936-1968

Source: Stimson and Oppenheimer (1982)

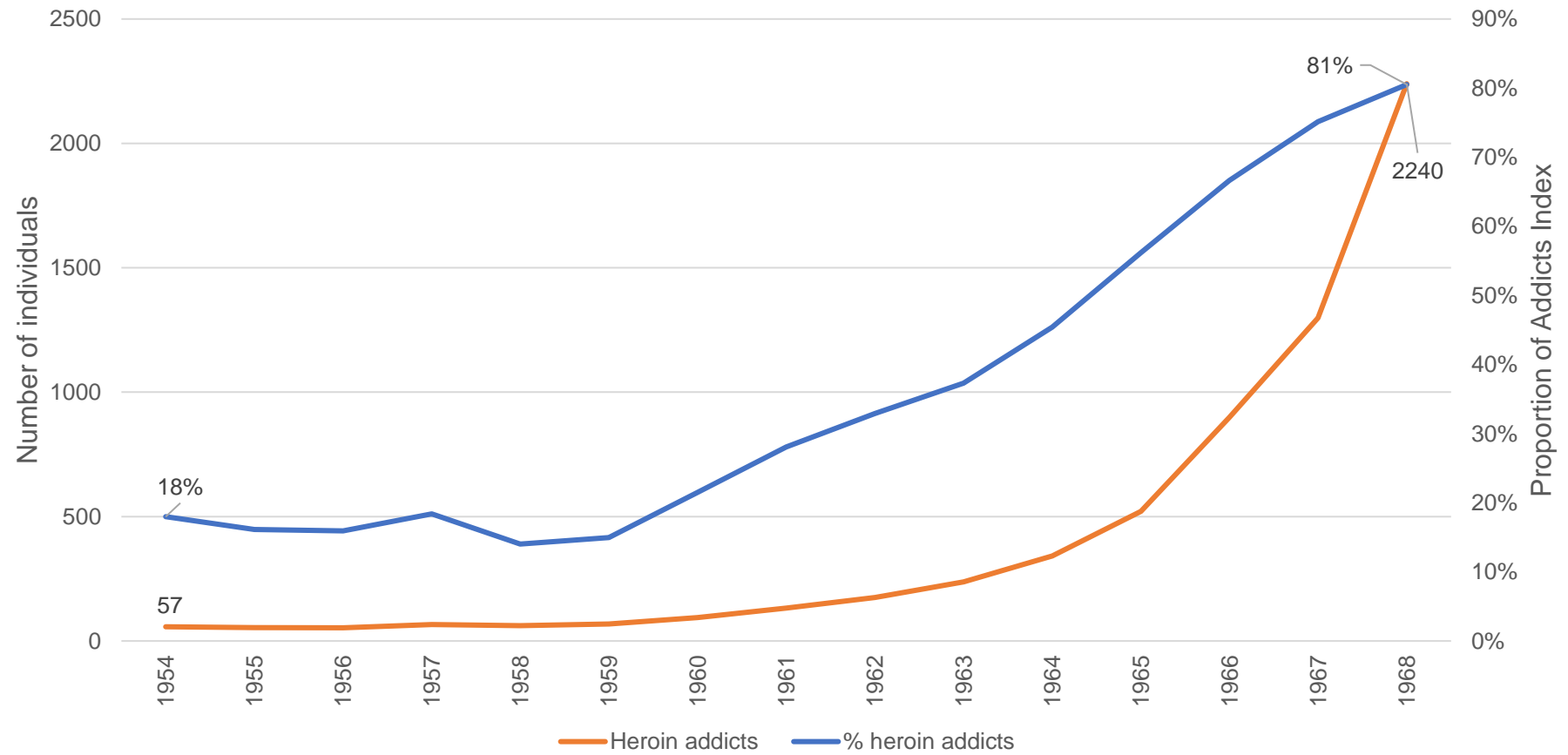


Figure 1.2 The number and proportion of heroin addicts recorded on the Home Office Addicts Index, 1954-1968

Source: Stimson and Oppenheimer (1982)

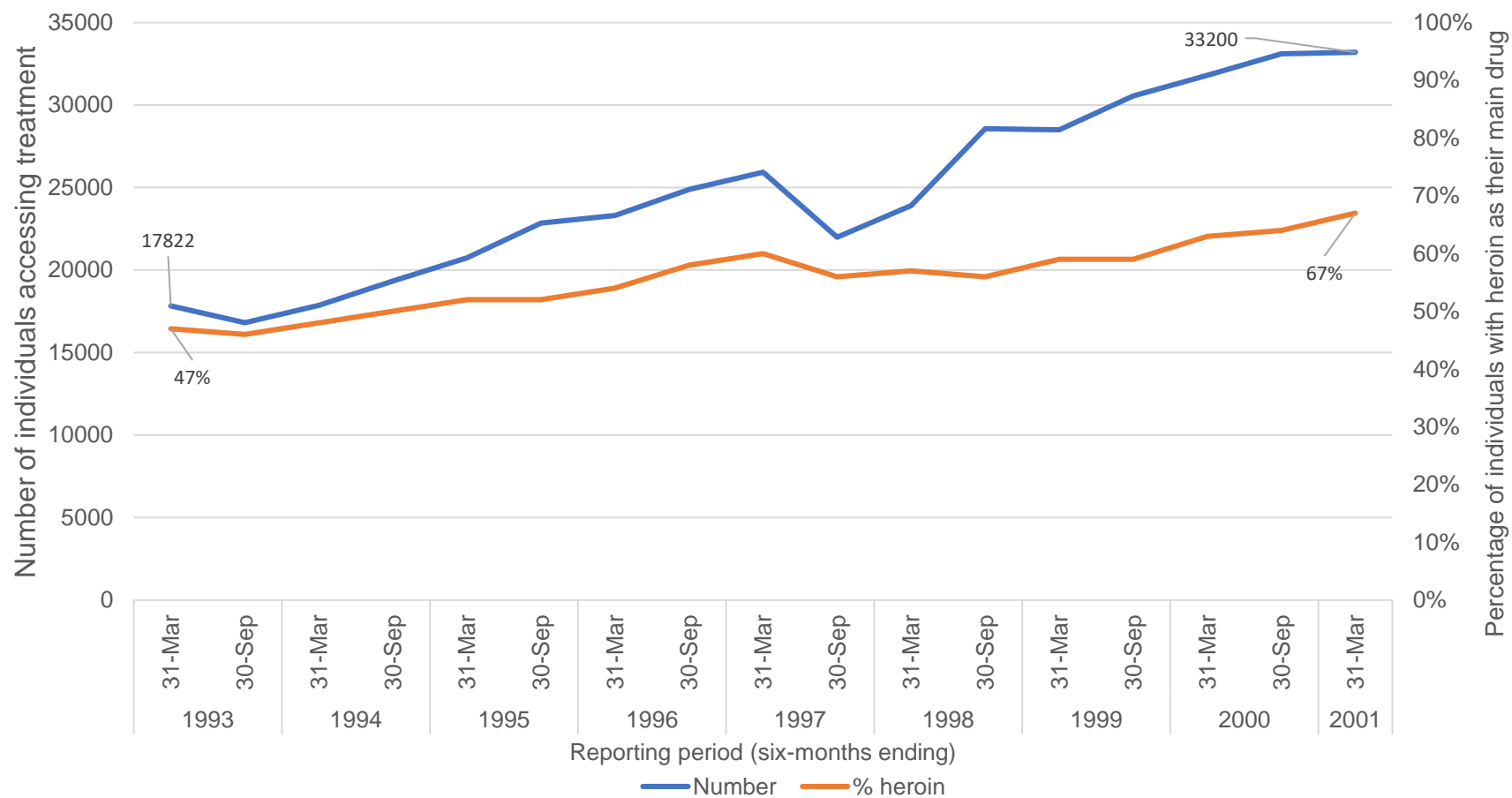


Figure 1.3 Statistics from the Regional Drug Misuse Database (1993-2001)

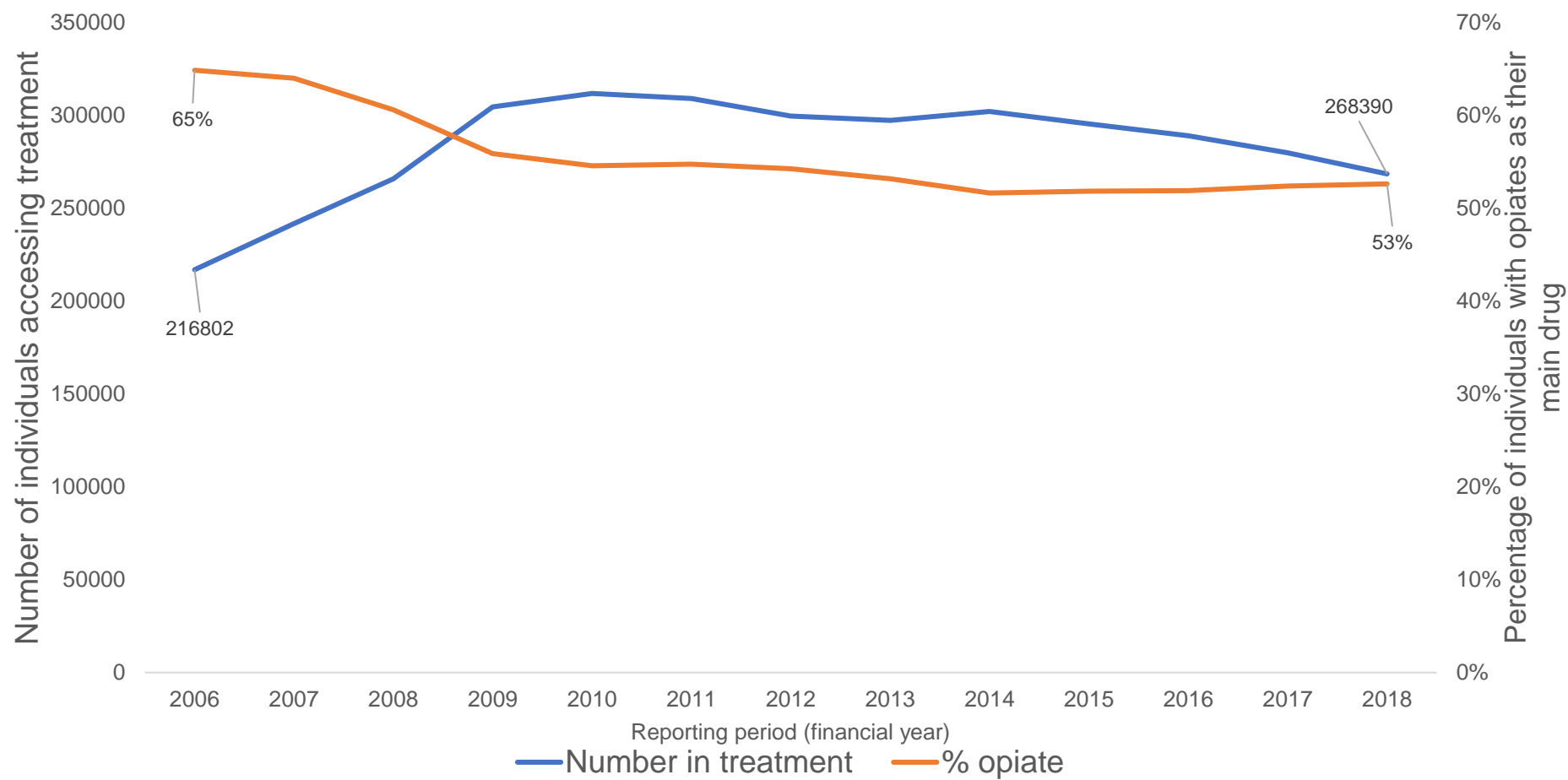


Figure 1.4 Statistics from the National Drug Treatment Monitoring System (2005/06-2016/17)

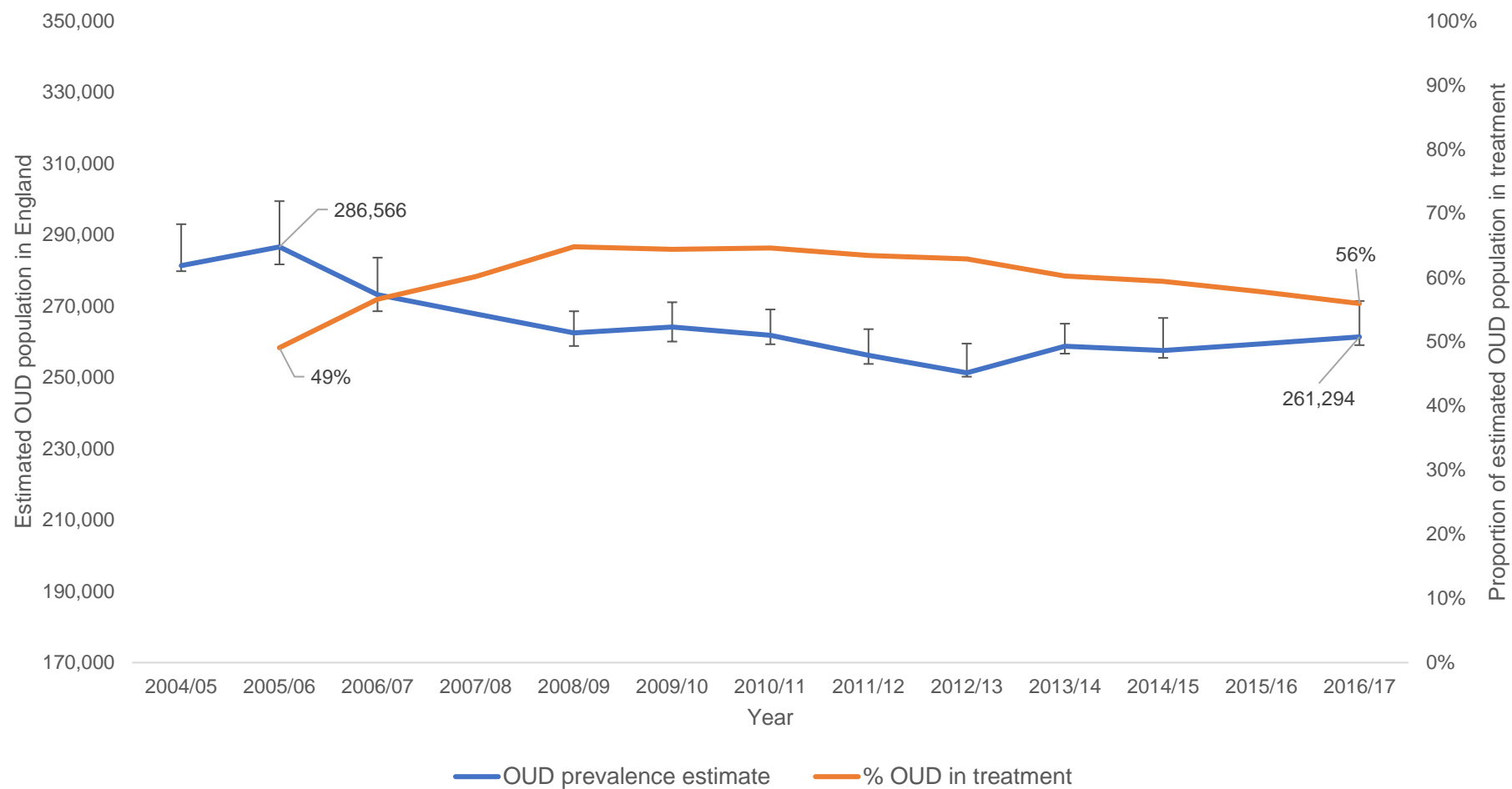


Figure 1.5 Estimated population of OUD in England and the proportion accessing treatment, 2004/05-2016/17



Figure 1.6 Regional variation in rate of opioid users per 1,000 population aged 15-64 (2016/17)

1.2 SEQUELAE OF OPIOID USE DISORDER

As outlined in **Table 1.1** and **Table 1.2** above, the consequences of OUD are manifold.

Aside from the expensive daily cost of paying for heroin – which generally requires significant time spent in illicit activities to fund the purchase of the drug – the person continues to use despite the numerous and persistent social, occupational, physical and psychological problems that are caused or exacerbated by such continuation. The Heroin Use Consequences Survey, for example, lists 21 negative sequelae arising from heroin use (Woodcock et al., 2015). While these sequelae have recently been shown to exist in five distinct domains (Moses et al., 2018), the following section will touch briefly on three main categories: criminal offending, morbidity and mortality.

1.2.1 CRIMINAL OFFENDING

The cost of maintaining a heroin addiction is substantial, with estimates of around £900-£1,000 per month in England (Hayhurst et al., 2013; Luty et al., 2009). Similar expenditure, around \$1,100, has been noted in Manhattan (Golub and Johnson, 2004). More recently, it has been estimated that the average monthly expenditure on heroin in the United States increased from \$1,240 in 2006 to \$1,450 in 2016 (Midgette et al., 2019). With less than 20% of patients with OUD in gainful employment in England (Public Health England, 2017a), many turn to acquisitive crime to pay for the drug. In a recent linkage study combining the NDTMS with the Police National Computer, more than a quarter of male opioid users had a recent criminal conviction for shoplifting, which increased to more than a third of their female counterparts (Pierce et al., 2015b). Other forms of offending, such as burglary and handling stolen goods were also prevalent in men. For females opioid users, a little over 2% were convicted of prostitution, rising to almost 7.5% in those using both opioids and crack cocaine (ibid). It is important to note that these are proven offences only; many offences go undetected or do not result in criminal convictions. Indeed, 40% of patients self-

reported offending behaviour in the past 30 days alone (Hayhurst et al., 2013). While accurately capturing the degree to which individuals with OUD engage in criminal activity is an inherently difficult endeavour, it is interesting to note that as of 31st March 2018 there were 11,453 individuals in receipt of prison-based specialist addiction treatment for heroin addiction problems out of a population of 83,263 prisoners (Ministry of Justice, 2018; Public Health England, 2018b). In other words, more than one in eight of the prison population were being treated for heroin addiction problems on that particular date.

1.2.2 MORBIDITY

Recurrent use of opioids is associated with an increased risk of developing a number of physical and mental health conditions, which contribute significantly to the burden of disease associated with OUD (Degenhardt and Hall, 2012). In this section, a brief overview of the main areas of morbidity is provided.

1.2.2.1 INFECTIONS

Opioid users, as a result of sharing injecting equipment, are at increased risk of contracting a number of infections, which, left untreated, can lead to compromised physical health. Fungal infections, though rare, have been reported (Hadley et al., 2017; Jensenius et al., 1999; Melnychuk and Sole, 2017). Bacterial infections can include endocarditis, wound botulism, tetanus, bacterial pneumonia and tuberculosis (Anderson et al., 1997; Beeching and Crowcroft, 2005; Duberstein and Kaufman, 1971; Frontera and Gradon, 2000; Hahné et al., 2006; Iqbal, 2001; Kalka-Moll et al., 2007; Louria, 1967; Neufeld et al., 1976; Passaro et al., 1998; Wang et al., 2006; Warner-Smith et al., 2001; Yuan et al., 2011). It has been estimated that 34,000 injecting drug users in England need care for injecting-related wounds, such as abscesses, and that around 18,000 need hospitalisation costing £19-30 million (Hope et al., 2008).

Injecting drug users are also at heightened risk of contracting viral infections, such as hepatitis B (HBV), hepatitis C (HCV) and HIV (Alshomrani, 2015; Garten et al., 2004; Mwatelah et al., 2015; Sepúlveda-Arias et al., 2014; Vallejo et al., 2015). HCV attacks the liver and can cause serious complications such as cirrhosis and liver cancer, although the virus can prove asymptomatic until the liver is severely damaged (Public Health England, 2018c). Globally, it is estimated that around 1% of the total population is living with HCV, equating to some 71 million people, while an estimated 257 million people are living with HBV (World Health Organization, 2017). In England, it is estimated that 203,000 (0.67%) people aged 15-59 have HCV (Harris et al., 2012) although the prevalence, at 22% in 2017, is much higher in injecting drug users (Public Health England, 2018c). Chronic infection occurs in around 85% of those with acute HCV (Hoofnagle, 1997). Individuals living with HCV can also experience fatigue, which appears to be multidimensional in nature and encompasses physical, cognitive, and affective dimensions (Glacken et al., 2003). Significantly, there were 1.34 million deaths estimated to have occurred as a result of viral hepatitis in 2015, 96% of which were due to HBV and HCV (World Health Organization, 2017). To put this in context, hepatitis caused around 300,000 more deaths than HIV (World Health Organization, 2017), yet hepatitis C is now a curable condition. The cost of treatment has fallen dramatically in recent years, from £35,000 in England per patient to £5,000 per patient (Hurley, 2018). With this cost reduction, the goal of eliminating hepatitis as a public health threat by 2030 (World Health Organization, 2016b) may well be achievable.

1.2.2.2 MENTAL ILLNESS

Prolonged heroin use is also associated with significant comorbid mental health disorders, including anxiety, depression and post-traumatic stress disorder (Darke et al., 2009; Han et al., 2010; Rosen et al., 2008; Sordo et al., 2012). It is likely these

underlying mental health issues play a significant role in the high rates of self-harming behaviour associated with OUD (Darke et al., 2010; Pérez de los Cobos et al., 2009).

1.2.2.3 NON-FATAL OVERDOSE

While overdose is clearly a major cause of death, non-fatal overdose can also engender long lasting consequences in the form of brain damage and cognitive impairment through prolonged hypoxia (Darke et al., 2007a). Other complications can include oedema, pneumonia, cardiac and muscular effects (Warner-Smith et al., 2001). The likelihood of users experiencing such an overdose is high. In an 11-year follow up of an Australian cohort, two-thirds had experienced at least one overdose and a quarter had experienced five or more overdoses (Darke et al., 2015).

1.2.3 MORTALITY

Globally, the estimated number of deaths attributed to OUD rose from 94,200 (95% CI 90,500-99,700) in 2005 to 121,100 (95% CI 109,500-129,700) in 2015, representing over 70% of deaths attributed to drug use disorders (GBD 2015 Mortality and Causes of Death Collaborators, 2016). It has been estimated that opioid use leads to the loss of 18 years of life (Smyth et al., 2007). In England and Wales, drug-related deaths (DRD) have been rising steadily since 2012, and deaths recorded in 2017 (n=3,765) are the highest recorded since comparable recording began in 1993 (n=2,178)(Office for National Statistics, 2018a). Opiates are the predominant substance (53%) recorded on the death certificate, with heroin/morphine accounting for 31% of the recorded DRD in 2017. OUD is also associated with an increased risk of suicide (Darke et al., 2010; Darke and Ross, 2002; Degenhardt and Hall, 2012; Pan et al., 2014).

Large-scale national linkage studies demonstrate that opioid users face a substantially increased likelihood of mortality. The standardised mortality ratio (SMR) is a measure of the extent to which a given population is at an increased risk of death relative to

what is expected from the general population sharing the same age and gender distribution. In a meta-analysis of 58 studies, Degenhardt et al. (2011) report a pooled SMR of 14.7 (95% CI 12.8-16.5), indicating that opioid users are almost 15 times more likely to die than would otherwise be expected.

In one study of nearly 200,000 opioid users (Pierce et al., 2015a), it was estimated that males have an SMR of 5.5 (95% CI 5.3-5.6) and females have an SMR of 6.9 (95% CI 6.5-7.4). The same study showed that while drug-related poisonings (i.e. fatal overdose) accounted for 43% of all deaths, opioid users were at a heightened risk of death from numerous causes, including: infectious/parasitic diseases (SMR 12.6, 95% CI 10.8-14.8); liver cancer (SMR 9.2, 95% CI 6.7-12.7); respiratory system (SMR 8.9, 95% CI 7.9-10.1); musculoskeletal system and connective tissue (SMR 4.5, 95% CI 2.6-7.9), and the circulatory system (SMR 3.1, 95% CI 2.8-3.4). Opioid users are also more susceptible to death by homicide (SMR 12.2, 95% CI 9.8-15.3). The increased risk of all-cause mortality has been documented in several countries, including: Spain (Jimenez-Treviño et al., 2011); Israel (Rosca et al., 2012); Taiwan (Huang and Lee, 2013), and the U.S. (Evans et al., 2015; Lopez-Quintero et al., 2015). Comorbid personality disorder and alcohol use disorder increase the risk of all-cause mortality (Bogdanowicz et al., 2015). Given the multitude of cause-specific mortality risks, it is not surprising that approximately half of opioid users are dead within 30 years (Grella and Lovinger, 2011; Hser Y et al., 2001).

One particular concern involves prisoners with OUD who face a substantially increased risk of fatal overdose on release. While there is some evidence of an increased risk across the first year (Kinner et al., 2013), the heightened risk is most notable in the first four weeks following release (Farrell and Marsden, 2008; Merrall et al., 2010).

Physiologically, the most likely mechanism involves the partial or complete eradication

of opioid tolerance during the incarceration period. Should an ex-prisoner administer a 'normal' pre-incarceration dose i.e. a dose they can no longer tolerate, there is a high probability that respiratory depression will set in leading to hypoxia and death. A return to injecting behaviour would further increase opioid bioavailability and thereby increase the risk of respiratory depression. The concurrent use of alcohol (Hill et al., 2016) and benzodiazepines (McCowan et al., 2009) may also exacerbate this effect.

Another area for concern is the relationship between age and methadone-specific mortality. The first study to demonstrate this effect was based on a Scottish cohort of more than 30,000 patients (Gao et al., 2016) and showed that, relative to those aged 25-34, those aged 45 or more had an adjusted hazard ratio (aHR) of 2.9 (95% CI 2.1-3.9). These results were confirmed in a large linkage study of 130,000 patients in England, which showed an increased risk of methadone-specific mortality for this age group (aHR 5.1; 95% CI 3.6-7.2) but no increased risk was identified for heroin-specific mortality (aHR: 1.1; 95% CI 0.8-1.5; Pierce et al., 2018).

Further complications associated with age have recently been reported (Advisory Council on the Misuse of Drugs, 2019). Ageing opioid users suffer from an accumulated burden of physical impairments and mental health problems, which exacerbates and complicates the effects of ageing. Older opioid users are, for example, at increased risk of mortality due to circulatory and digestive diseases (Gao et al., 2019). The report also highlights that ageing opioid patients are more difficult to treat, have entrenched problems, their dependence is harder to overcome and they are less able to access other services such as housing, dental care and counselling. Recognising that the ageing cohort is rapidly growing as a proportion of patients accessing treatment, the report also recommends that treatment provision needs to be adapted to meet the increasingly complex needs of this group.

1.3 TREATING OPIOID USE DISORDER

The provision of treatment for persons involved in the “abuse of drugs” is set out in Article 38 of the Single Convention on Narcotic Drugs (United Nations, 1961), but it was not until 1968 that the first dedicated treatment centres were established in Great Britain (Merry, 1975). In the fifty years since then, the majority of countries with a high prevalence of OUD have developed an array of treatment services. The opioid medication methadone has been a front-line treatment since the establishment of treatment centres in Great Britain and, since the late 1990s, buprenorphine has also become a front-line treatment (Mattick et al., 2014, 2009). Both medications are randomised-controlled trial supported pharmacotherapies which are typically provided by specialist community, primary care and hospital providers. Inpatient withdrawal management and drug-free residential rehabilitation services are also available. In addition to case management, national clinical guidelines recommend additional psychosocial interventions to address cognitive and behavioural symptoms of OUD (e.g. National Institute for Clinical Excellence, 2007). Some OUD patients receive psychosocial interventions without an opioid medication.

1.3.1 A NOTE ON SPONTANEOUS RECOVERY

Spontaneous recovery, or natural recovery, refers to the process of overcoming OUD in the absence of treatment. The first report of this phenomenon emerged in the early 1960s when it was suggested, from examination of records submitted to the US Federal Bureau of Narcotics, that registered addicts tended to disappear from records after the age of 35-40 (Winick, 1962). At the time, Winick claimed that “...it is almost impossible for a regular user of narcotics to avoid coming to the attention of the authorities within a period of about two years”, although this claim was shown to be largely inaccurate a decade later when it was demonstrated that a quarter of active users can quite readily avoid the official register (Vaillant, 1973).

Nonetheless, several small-scale studies were published in the 1960s and 1970s that suggested that spontaneous recovery was possible (Waldorf and Biernacki, 1979). Perhaps the most compelling evidence for spontaneous recovery involved following up soldiers returning from the Vietnam war (Robins, 1974; Robins et al., 1975, 1974). Robins and her team took a sample of around 900 soldiers from the 14,000 who returned from Vietnam in September 1971. Over 40% had tried either opium or heroin during their tour, and approximately 20% could be said to have OUD (although this diagnostic term was not in use at this time). A year after their return, however, only 2% were using heroin on a weekly basis. Numerous factors played a role in facilitating such dramatic recovery rates, including purity, price, route of administration, social norms, education and life circumstances (Hall and Weier, 2016).

For some drug users – usually those not deeply engrained in the drug using world – spontaneous recovery can be instigated when their central point of contact for accessing drugs is no longer available, for example when a spouse is imprisoned or dies (Biernacki, 1990). For others, they first need to develop a sense of resolve to stop using drugs and develop alternative social connections or coping strategies. This resolve can develop in response to hitting ‘rock bottom’ or experiencing an existential crisis, but these are not in themselves pre-requisites for change (Waldorf and Biernacki, 1981).

This resolve, or motivation to change, followed by active participation in the decision to change, as well as maintaining the change are three stages of change outlined by Klingemann (1991). Other models of change include two precursor stages, precontemplation and contemplation (Prochaska et al., 1992), which describe a stage in which there is no desire to change, or indeed see the need for change, and a stage

in which the problem is recognised and action is probably required but a firm decision to change has not yet been reached.

While recovery in the absence of treatment is possible, it has recently been shown, at least in the case of heroin, that almost all (~90%) individuals who recover have utilised treatment services (Cunningham, 2000). Comparisons between those who have and have not undergone treatment in their process of recovery show that those recovering without treatment tend to have experienced fewer difficulties in high school, were incarcerated less since leaving high school, more likely to have a college education and less likely to be unemployed (Graeven and Graeven, 1983). Those accessing treatment also appear to have more mental health issues (Rounsaville and Kleber, 1985). In other words, those seeking treatment are more chaotic. Other researchers (Power et al., 1992) have reported that those in treatment have similar levels of heroin use to those not seeking help, but the former group had significantly more concerns across a range of issues, such as finance and health. Power et al. concluded that this provided evidence for the need for low-threshold outreach programs to engage heroin users not yet engaged in treatment.

1.3.2 LARGE-SCALE COHORT STUDIES

In their seminal work outlining the case for methadone treatment, Dole and Nyswander (1965) assessed a sample of just 22 patients in New York. In the 50 years since then, large scale national prospective cohort studies have consistently demonstrated that treatment is associated with reductions in opioid use, drug injecting and criminal offending, together with improvements in employment, health and social functioning.

The US initiated these OUD cohort studies (Craddock et al., 1997; Hubbard et al., 1989; Sells et al., 1976) and were followed, in turn, by England (Gossop et al., 1997),

Australia (Ross et al., 2002), Scotland (McKeganey et al., 2008) and Ireland (Comiskey et al., 2009). Commonly, a large cohort of patients accessing treatment is identified and recruited into a long-term prospective follow-up study. All, or a sample of, patients are re-interviewed at various points following recruitment. Crucially, participation in the follow up interviews is not contingent on being continuously enrolled in treatment.

It is important to note that while the randomised control trials (RCTs) are often held as the pinnacle of research designs (Concato et al., 2000; Sacks et al., 1982), it can also be argued that the design is inappropriate or unethical in the context of researching drug treatment effectiveness should this require the randomisation of treatment seekers to a no treatment condition. That said, there are a number of variants of the RCT design. RCTs designed to determine whether or not a new treatment has a different degree of efficacy than the current standard (or placebo) is known as a 'superiority trial' while RCTs designed to determine whether or not a new treatment yields similar efficacy as the current treatment standard is known as an 'equivalence trial' (Christensen, 2007). The equivalence trial is appropriate when the new treatment is associated with fewer side effects, or is simpler to administer or is perhaps cheaper to deliver, and it is not expected to deliver a larger effect than the control treatment being compared against. Related to the equivalence trial is the 'non-inferiority trial' (Christensen, 2007). Whereas the equivalence trial aims to determine whether the new treatment falls within plus or minus a certain level of efficacy as that obtained from the current treatment standard, the non-inferiority trial is concerned only with testing whether the new treatment is at least as good as minus a certain level of efficacy. The advantage the non-inferiority trial design has over the equivalence design is that it requires fewer participants and is therefore cheaper to run.

Regardless of the type of RCT, it is relevant at this point to highlight that ‘efficacy’ is the term used to describe the performance of a given intervention under the idealised RCT conditions (Singal et al., 2014). That is to say, RCTs often benefit from particularly stringent inclusion/exclusion criteria and can be, in the case of a psychosocial intervention for example, staffed with more experienced or more highly trained individuals than one would normally expect under routine conditions. Performance of an intervention under these routine conditions is referred to as treatment effectiveness and it is often the case that efficacy surpasses effectiveness (Singal et al., 2014).

Nonetheless, it remains problematic for cohort studies to attribute changes in patient behaviour wholly to the treatment exposure as there may be a number of self-selection or other unmeasured biases affecting outcomes. Replication of treatment effectiveness outcomes across large scale multinational multisite studies do, however, lend credence to a general finding that ‘treatment works’ (Hubbard et al., 1989; McKeganey et al., 2008).

1.3.2.1 DRUG ABUSE REPORTING PROGRAM

The Drug Abuse Reporting Program (DARP) was the first in a series of global longitudinal cohort studies examining the effectiveness of treatment under routine conditions. A cohort of almost 44,000 people were recruited from 52 sites across the US between 1969 and 1974. Numerous post-treatment follow-up studies were conducted between one and three years (Sells et al., 1976; Sells and Simpson, 1980; Simpson, 1981, 1980, 1979; Simpson et al., 1979; Simpson and Sells, 1982), and culminated in a 6-year (Simpson et al., 1982) and 12-year follow-up (Simpson and Sells, 1990).

1.3.2.2 TREATMENT OUTCOME PROSPECTIVE STUDY

The Treatment Outcome Prospective Study (TOPS) recruited 11,750 patients between 1979 and 1981 across 41 drug treatment programs in the US (Hubbard et al., 1989). Patients were interviewed at intake, at regular intervals during treatment and then at a number of periods following treatment, including three months, one year, two years and three-five years. Detoxification only patients were dropped from treatment effectiveness reporting, yielding a final sample of 9,989 patients accessing outpatient methadone (n=4,186), residential (n=2,891) and outpatient drug-free (n=2,914) services.

1.3.2.3 DRUG ABUSE TREATMENT OUTCOME STUDY

The Drug Abuse Treatment Outcome Study (DATOS), again in the US, recruited 10,010 patients across 91 programs and 11 sites between 1991 and 1993. As DATOS was specifically designed to utilise many of the same measures as captured in TOPS, as well as similar outpatient methadone, outpatient drug-free and residential programs, comparisons between the two studies can be drawn (Craddock et al., 1997). Across all three treatment modalities, there were significant increases in the weekly use of cocaine and there was a lower proportion of patients engaged in full time employment.

Interestingly, the findings of these three cohort studies are still relevant today. Public Health England continue to monitor engagement in 'effective treatment', which is defined by patients being continually enrolled in treatment for at least three months. This is directly influenced by DARP, TOPS and DATOS, which showed that patients who experienced at least 12 weeks of treatment experienced more favourable one-year outcomes, although it should be noted that few significant differences by treatment duration were noted at five-years (Hubbard et al., 2003; Simpson, 1979).

1.3.2.4 NATIONAL TREATMENT OUTCOME RESEARCH STUDY

The National Treatment Outcome Research Study (NTORS) was commissioned by a Department of Health Task Force in 1994 to investigate whether, and to what degree, the outcomes reported by the U.S. studies would apply to patients accessing treatment in the United Kingdom. A total of 1,075 patients were recruited in 1995 across 54 treatment agencies. Treatment outcomes were reported at six months, 1 year, 2 year and 4-5 years following intake (Gossop et al., 2003, 2002, 2000, 1997). The NTORS project was influential in instigating similar research endeavours in Scotland, Ireland and Australia, and the research played a key role in the drug treatment policy making of the late 1990s and early 2000s (Gossop, 2015).

1.3.2.5 DRUG OUTCOME RESEARCH IN SCOTLAND

The Drug Outcome Research in Scotland (DORIS) study recruited a sample of 1,033 drug users from 28 community and five prison treatment agencies across Scotland in 2001-2002 (McKeganey et al., 2008). In a similar manner as TOPS, patients who were recruited from needle exchange only agencies were dropped from outcomes reporting (n=26). Patients were followed up at eight, 16 and 33 months.

1.3.2.6 RESEARCH OUTCOME STUDY IN IRELAND

The Research Outcome Study in Ireland (ROSIE) study is the smallest of the national cohort studies, having recruited 404 patients from 44 treatment agencies. Alongside drug use outcomes, ROSIE also examined the effectiveness of treatment for health, social functioning, harm, mortality and crime outcomes. Patients were followed up at 1-year and 3-years, and 72% completed all three interview assessments.

1.3.2.7 AUSTRALIAN TREATMENT OUTCOME STUDY

The Australian Treatment Outcomes Study (ATOS) recruited 615 heroin users between 2001 and 2002. Participants were selected from the following four main treatment modalities: methadone/buprenorphine maintenance (n=201), detoxification (n=201),

residential rehabilitation (n=133) and a non-treatment group (n=80). Originally envisaged to examine treatment outcomes and costs at three and 12 months, the project was extended to capture further outcomes at 2-years, 3-years and 11-years (Ross et al., 2002; Teesson et al., 2015).

1.3.3 LONG TERM HEROIN USE OUTCOMES

Presented in **Figure 1.8** is the proportion of patients reporting opioid use in each of the large-scale national studies. Of note is the variability opioid use reported at baseline. The four cohorts reporting approximately 30% of opioid use or less were from the TOPS and DATOS studies, and reflect patients accessing either residential or drug-free treatment programs. Both DARP and ATOS report almost 100% of their cohorts as using opioids in the period preceding study enrolment.

To a varying extent, each study demonstrates a general reduction in opioid use over time, with the most change occurring in the first 6-12 months. This trend has been referred to as the 'rush and trickle' of treatment outcome (Finch, 2003). Part of the variability is attributable to the length of time at the assessment points for which opioid use prevalence is measured. The various studies examine heroin use across 30 day (ATOS), 90 day (NTORS, DORIS, ROSIE) or full year (DARP, TOPS, DATOS) periods.

1.4 OUTCOME MONITORING SYSTEMS

It has been suggested that the conceptualisation, treatment and evaluation of addiction needs to shift from an acute-care model to a chronic-care one (McLellan et al., 2005). McLellan's conceptualisation sees drug addiction closely resemble the course of other chronic illnesses such as diabetes, asthma and hypertension. Assessing completion rates and status post-treatment for some interventions such as residential rehabilitation or in-patient treatment is appropriate, but some community setting interventions require an evaluation approach which needs to look beyond the short-term and include longer-

term follow-up during which patients may flow in and out of the treatment system. This can be achieved through an integrated, standardised, and electronic outcomes monitoring system (OMS).

This composition of treatment interventions delivered in England, with more than 90% of treatment delivered under outpatient conditions (Public Health England, 2016a) is similar to that of the US (McLellan et al., 2005). England is, however, in the unique position of having a national OMS currently in place.

OMS “reflects a fundamental organizational and professional value, namely, a commitment to quality, fact-based treatment” (Brown et al., 2003). The OMS becomes a positive feedback loop where the impact of routine treatment on outcomes is monitored, reported, and informs future clinical and commissioning decision making. Successfully implemented OMS allow for the early detection of problems in key performance indicators, expose opportunities for service improvement, and improve outcomes.

In 1998, the US funded the development and automation of OMS in 19 states (Evans and Hser, 2004), including California (ibid), Iowa (Hedden et al., 2012), Minnesota (Harrison and Asche, 2001), and Washington (Luchansky et al., 2000), and Canada implemented an OMS in Ontario (Rotondi and Rush, 2012). In England, all individuals accessing publically funded drug treatment are asked to share a core dataset with the National Drug Treatment Monitoring System (NDTMS), held by Public Health England (PHE), and over 98% consent to do so (Marsden et al., 2009).

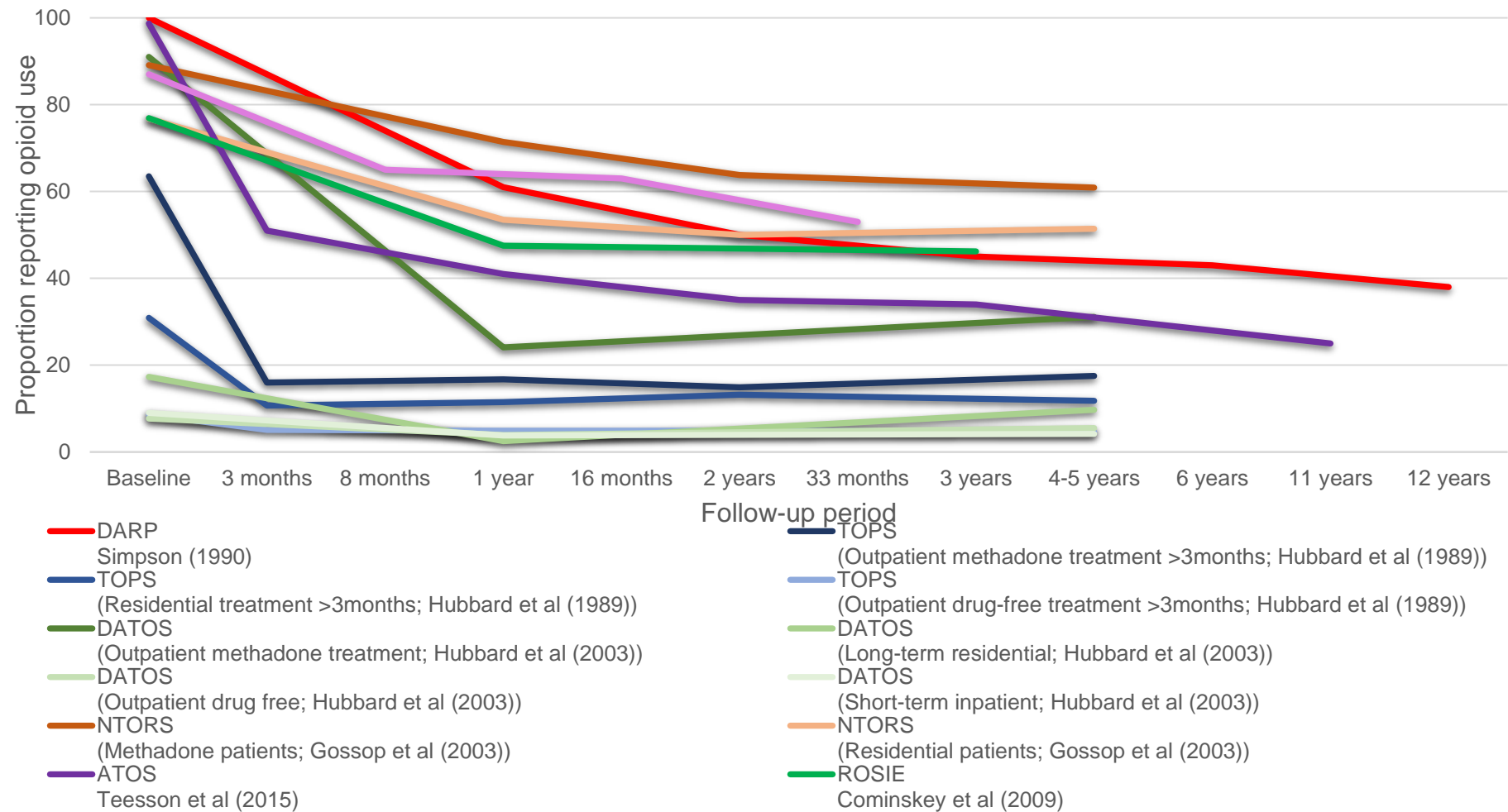


Figure 1.1 Proportion of patients reporting opioid use over time

1.5 DEVELOPMENT OF THE TREATMENT OUTCOMES PROFILE

NDTMS was originally designed to capture intelligence on the number of people in treatment, interventions received, substances targeted for treatment, together with measures of process such as waiting times and the successful completion of treatment, a proxy outcome of recovery. In 2006, however, at the request of national stakeholders in England, the then National Treatment Agency for Substance Misuse sought to include a minimum set of behavioural indicators that would be measured throughout a patient's time in treatment. A team of clinicians, academics and policy makers was convened, including me as a research assistant, and it was decided that a new instrument was justified to adequately reflect the priorities of the then national drug strategy.

In total, more than 1,000 patients were recruited from 113 specialist treatment services that delivered OST, psychosocial and residential-based interventions. From a pool of around 80 potential items to be included on the new instrument, 38 were considered to be the most relevant following discussions with patients, service providers and other professionals. These items concerned four principal domains including substance use, health risk behaviours, offending and health and social functioning. The procedure included three interviews: an initial assessment, a 7-day retest (involving a different keyworker) and a 1-month follow up. This enables the psychometric evaluation of test-retest reliability, concurrent validity and change sensitivity. The final result was the 20-item Treatment Outcomes Profile (TOP: Marsden et al., 2008). The TOP is a short, structured, clinically-administered set of twenty questions which measures substance use, health and social functioning information recorded as part of on-going delivery of care. The TOP was incorporated into NDTMS in October 2007, the point at which NDTMS evolved into an outcomes monitoring system. Since then, other countries have followed suit and, at the time of writing, there now exists a locally validated version of

the TOP in Chile, China and Australia (Castillo-Carniglia et al., 2015; Ryan et al., 2014a; Wang et al., 2017)

Research using NDTMS-based TOP data has, to date, focused on developing methods to capture change in the treatment seeking population (Marsden et al., 2011), evaluating performance while statistically adjusting for heterogeneity in the population (Marsden et al., 2012b), and reporting early (six-month) in-treatment reductions in opioid and crack-cocaine use (Marsden et al., 2009).

1.6 SUCCESSFUL COMPLETION OF TREATMENT

Treatment outcome studies can be expensive and time consuming and the commissioners of publicly funded treatment systems want regular reports on the effectiveness of services. While unsanctioned discharge (drop-out) from treatment and retention have been used (Brorson et al., 2013; Stark, 1992; Faggiano et al., 2003), a frequently used measure in the literature on human services research is the proportion of patients treated who complete treatment successfully (Alterman et al., 2001).

Successful completion of treatment is associated with reduced drug use (Evans et al., 2009; Kornør and Waal, 2005), increased employment (Evans et al., 2009; Sung and Chu, 2011; TOPPS-II Interstate Cooperative Study Group, 2003; Zarkin et al., 2002; Lang and Belenko, 2000; Finnigan, 1996), lower arrests and incarceration (Gifford et al., 2014; Evans et al., 2009; Campbell et al., 2007; Finnigan, 1996), and a reduced likelihood of readmission to treatment services (Luchansky et al., 2000). These indicators of treatment system effectiveness can reveal differential response between populations. For example, drop-out is more likely in those with greater psychiatric severity and those with more arrests in the year preceding treatment, and less likely in those living with dependent children and those receiving residential treatment (Evans et

al., 2009). Ethnic minority populations may have a lower rate of treatment episode completion than their white counterparts (Mennis and Stahler, 2016).

Successful completion of treatment captures only one facet of the OUD recovery process. Relapse is common (e.g. for 60% within six months after leaving treatment in one US study; McLellan et al., 2005). The process of achieving a stable recovery can involve several treatment cycles over the course of a decade (Dennis et al., 2005; Hser et al., 1997). To fully assess the effectiveness of treatment systems, national administrative databases need to be able to capture this process, but the requirements of such systems are difficult to implement. In the US, the absence of patient consent prevents linkage across consecutive treatment episodes in the Treatment Episode Data Set, operated by the Substance Abuse and Mental Health Services Administration. The impact of this is twofold: it is not possible to objectively assess whether an individual has previously engaged in treatment (an indicator of patient-level complexity; Marsden et al., 2012b); it is also not possible to determine whether a patient's successful completion status is enduring or transient.

1.7 SUB-POPULATION ANALYSIS

In 1967 the Addiction Research Unit was established at the Institute of Psychiatry in London at the behest of the then Minister of Health. This multidisciplinary team instigated a 10-year follow up study of patients accessing the new treatment Clinics in 1969. They took a sample of 128 patients, which represented around 12% of all patients accessing treatment at the time (Stimson and Oppenheimer, 1982). Although still relatively small in number, this study was the first in-depth analysis of treatment effectiveness in England. A typological approach was undertaken using cluster analysis and patients were identified as belonging to one of four behavioural categories: 'stables', 'junkies', 'loners' and 'two-worlders' (Stimson, 1972). These groups differed

significantly on a number of domains, including employment, criminal involvement, hospitalisations and social connections with other addicts.

Unlike the variable-centred approach adopted by Stimson (1972), sophisticated person-centred methods to empirically derive sub-populations within cross-sectional and longitudinal data have been emerging in recent years (Asparouhov and Muthén, 2014; McCutcheon, 1987; McLachlan and Peel, 2000; Muthén and Muthén, 2000; Nagin, 2005). In the case of cross-sectional data, Latent Class Analysis (LCA) is a useful tool used to assign patients to a sub-group of patients who, more or less, share the same characteristics over several indicators which are collected at the same point in time.

At the start of treatment, an assessment of any given patient yields substantial information about their clinical history including, for example, concurrent substance use. Concurrent substance use typically involves the use of one or more of the following substances alongside heroin: alcohol, cocaine powder, smokeable (*crack*) cocaine and benzodiazepines (Darke and Hall, 1995; Harrell et al., 2012; Kuramoto et al., 2011; Monga et al., 2007). Identification of sub-populations is important as certain groups may vary with respect to drug-related harm. For example, heroin smokers who use crack cocaine are substantially less likely to be infected with Hepatitis C virus than those who inject heroin (Harrell et al., 2012). Opioid users with concurrent substance use have been observed to have greater health and social problems (Leri et al., 2003) and a relatively poorer response to OUD treatment (Williamson et al., 2006; Marsden et al., 2011, 2009).

Application of sub-population analyses to longitudinal data may distinguish between a sub-group of patients who respond well to treatment and another that does not.

Generally, studies examine longitudinal change at the cohort level in the aggregate, and tend to report a progressive response to treatment. In the national Australian study, the rate of heroin abstinence across one-, three- and 11-year follow-up was 59%, 66% and 75%, respectively (Teesson et al., 2015). Patients accessing methadone treatment in England also demonstrated growth in abstinence rates, albeit at a lower rate than the Australian study, rising from 14.1% at Year 1 to 24.3% at Year 2 and 25.7% by 4-5 years (Gossop et al., 2003). In the same study, patients accessing residential treatment appeared to make more substantial gains by Year 1 (46.5% abstinent), and then slowed in the rate of growth, with 48.6% abstinent by 4-5 years. In the US, abstinence actually reduced from 75.9% at one-year to 68.9% at five-years for patients accessing outpatient methadone treatment and from 97.5% to 90.3% for patients accessing long-term residential care (Hubbard et al., 2003).

These population averaged estimates, however, can mask differential response during treatment among OUD sub-populations. For example, in a large-scale English national study, 37% of adults with OUD achieved abstinence from opioid use within six months of initiating treatment while 31% improved, 3% deteriorated, and the remaining 29% did not reliably change their opioid use from admission (Marsden et al., 2009).

Disaggregation of response in treatment can also been approached longitudinally as a study of developmental trajectories. Employing latent growth statistical techniques with a sample of 471 male heroin users studied over 16-years, Hser and colleagues identified three classes (Hser et al., 2007). The majority were classified as 'stably high-level' users of opioids (59%), while a third (32%) were 'late-decelerated users' and a minority (9%) were 'early-quitters'. In a further 10-year study of heroin, cocaine and methamphetamine users five drug use trajectories were identified among 1,797 patients: 'high use' (30.3%); 'increasing use' (14.5%); 'decreasing use' (14.1%);

‘moderate use’ (35.5%), and ‘low use’ (5.6%)(Hser et al., 2008b). The authors noted that heroin users were disproportionally represented in the ‘high use’ group.

In an important study of change across 30 years, Grella and Lovinger (2011) reported that nearly half of their OUD cohort had died, and among survivors (n=486), four drug use trajectories were identified: approximately a quarter were classified as a ‘no decrease’ group; quarter comprised the ‘rapid decrease’ group; 35% formed a ‘gradual decrease’ group and the remaining 15% had a ‘moderate decrease’ response. In a recent report from Hser’s group, four groups were identified in a cohort of 795 patients enrolled in a treatment trial and followed up after 4.5 years (Hser et al., 2017). The majority formed a ‘low use’ group (42.0%), followed by ‘high use’ (22.3%), ‘decreasing use’ (18.6%) and ‘increasing use’ (17.1%) groups. Participants in the ‘decreasing use’ group spent more time in treatment across the follow up period than those in the ‘high use’ group. Comparable groups have been reported in Australian research. Teesson and colleagues identified six distinctive trajectories among 428 OUD patients (Teesson et al., 2017a). The largest group demonstrated ‘no decrease’ (22.1%), followed by ‘gradual decrease’ (21.5%), ‘gradual decrease to near abstinence’ (17.1%), ‘rapid decrease to maintained abstinence’ (16.1%). ‘rapid decrease with late relapse’ (15.8%), and ‘rapid decrease with rapid relapse’ (7.5%).

Several patient-level characteristics have been linked to developmental trajectories associated with a poor treatment response, including: males and people from some ethnic minorities, and among those with less educational achievement, greater behavioural problems, earlier involvement with the criminal justice system, earlier onset of drug use (Grella and Lovinger, 2011; Hser et al., 2008b, 2007). Membership of less responsive trajectories is associated with worse outcomes in terms of substance use,

mental health, physical health and mortality (Hser et al., 2007; Teesson et al., 2017a; Hser et al., 2017).

1.8 THESIS AIMS

This thesis presents a series of three linked analyses of the National Drug Treatment Monitoring System (NDTMS). Overall, this thesis will contribute to the evidence base for OUD treatment by examining a national cohort of patients admitted to treatment in England. It applies modern statistical techniques to identify sub-populations of OUD patients and estimates whether or not sub-populations at treatment entry or sub-populations over the course of treatment exhibit a differential likelihood of recovering from OUD.

AIM 1

To identify sub-populations of OUD patients at the start of treatment, using Latent Class Analysis, and to investigate whether, and to what degree, these sub-populations differ in completing treatment successfully over five years.

AIM 2

To identify longitudinal sub-populations of OUD patients based on their self-reported heroin use, through Latent Class Growth Analysis, in patients who have been continuously enrolled in opioid substitution treatment for five years and to estimate whether or not these sub-populations are predictive of eventually completing treatment successfully.

AIM 3

To identify sub-populations according to use of other substances routinely monitored in the course of treatment in England, including: alcohol, cannabis, crack cocaine, cocaine powder, amphetamines, and 'other drugs', to examine how these trajectories

relate to heroin use trajectories, and to estimate whether or not membership modifies the likelihood of completing treatment successfully.

Chapter 2 DESIGN AND METHODS

2.1 OVERVIEW

This thesis is based on data extracted from the National Drug Treatment Monitoring System (NDTMS). Patients included in this thesis were from all the local treatment systems in England and all the operational specialist community agencies in the NHS and third-sector providing pharmacotherapies, psychosocial interventions and adjunctive support services for OUD in community, in-patient (short-term medically supervised withdrawal), and residential (drug-free rehabilitation) settings. All adults (≥ 18 years) diagnosed with OUD who presented for treatment in England between 1 April 2008 and 31 March 2009 were selected.

As shown in Figure 2.1, 56,156 patients were referred to treatment in 2008/09. There were 1,799 patients (3.2%) who did not commence a single treatment intervention by 31 March 2014 and were therefore excluded from all analyses. The final cohort for Study 1 were those patients who were discharged from their index treatment journey during the five-year observational period ($n=45,467$; 85.5%). The remaining 7,890 patients (14.5%) were continuously enrolled in treatment for the five-year period. Of these, 171 patients were removed from further analysis as they had not completed the heroin use frequency item on the Treatment Outcomes Profile throughout the entire five-year period ($n=158$) or had not been continuously enrolled in OST for the five-year period, yielding a cohort of 7,719 patients for Study 2. For Study 3, two patients were removed due to missing data on all other substances on the TOP throughout the study period, leaving a final cohort of 7,717 patients.

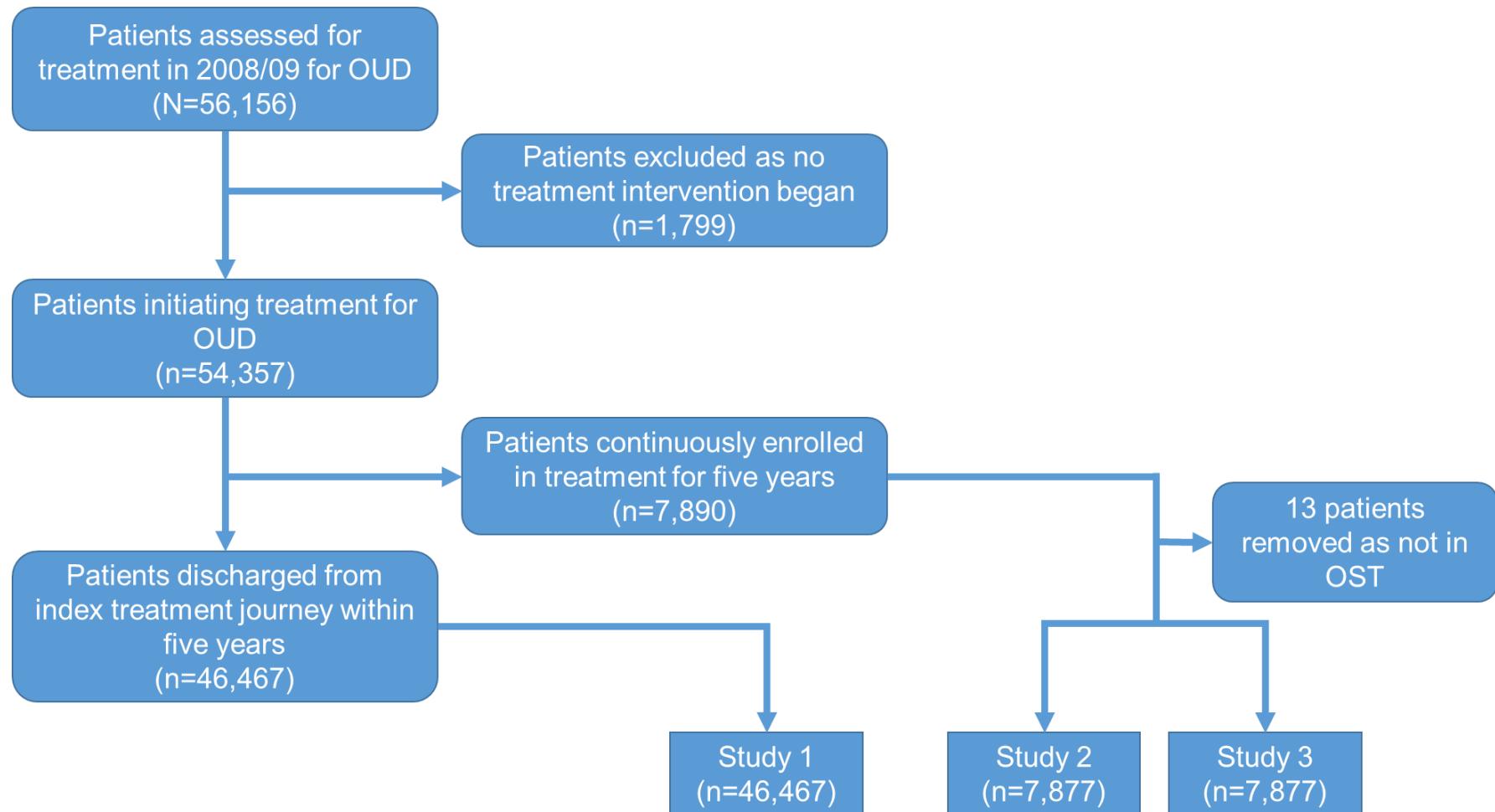


Figure 2.1 Data flow for studies

2.2 NDTMS

NDTMS is the England national core dataset of all clients accessing drug and alcohol treatment. All publically funded treatment agencies are required to submit data to NDTMS on a monthly basis. The system started in 2001 and has been operational since 2005. It has been managed by Public Health England (PHE) since 2013. Patient consent is required for data to be submitted to PHE, and over 98% of patients provide this consent (Marsden et al., 2009). As part of the consent process, patients also empower PHE to conduct research on treatment effectiveness (Public Health England, 2018d, 2018e).

NDTMS is designed to capture key information at each stage of the treatment process. A referral to treatment marks the start of the treatment process. Referrals into the treatment system can broadly be categorised into self-referrals, referrals from the criminal justice system and other referrals, such as accident and emergency departments or psychiatric units. During the first face-to-face meeting, an initial triage assessment is conducted by clinical staff. Where a treatment need is clinically indicated, the substance(s) and patient demographics are recorded on NDTMS and an appointment for a treatment intervention is arranged. For OUD patients, the average waiting time for the first intervention is 1.7 days and approximately 98% of patients start an intervention within three weeks (Public Health England, 2018a). All treatment interventions are recorded on NDTMS. Ongoing treatment is available for as long as is clinically indicated, until recovery from OUD is achieved, or a patient declines to partake in further treatment.

2.3 TREATMENT EPISODES AND JOURNEYS

Following the NDTMS reporting protocol, each patient-level 'treatment journey' comprised a single episode of pharmacotherapy or psychosocial intervention provided

by a clinic, enrolment in concurrently delivered medication and psychosocial interventions (from one or more clinics), or a continuing care package in which an intervention was followed by one or more further interventions. Episodes commencing after 21 days are classified as a new treatment journey (Public Health England, 2015a). Recovery support services are offered concurrently or following a treatment episode. Patients and treatment provisions are regularly reviewed and at the end of the 'treatment journey' patients who overcome their dependence are successfully discharged from the treatment system.

2.4 PATIENT IDENTIFIERS

As set out in the confidentiality documentation (Public Health England, 2018d, 2018e), NDTMS does not collect a patient's full name and address. Instead, it only collects patient initials, date of birth, gender, partial postcode and local authority of residence. This patient-level information forms part of every record submitted to NDTMS and is critical to constructing the patient entity on which all treatment provider, local authority and national statistics are generated.

2.5 MEASURES

2.5.1 TRIAGE ASSESSMENT

As part of the core dataset, NDTMS collects information on the patient demographic, clinical information and previous treatment exposure. Utilised throughout this thesis are the following triage covariates: sex, age, ethnicity, employment, homelessness, injecting status, years using heroin, referral route, and whether or not a patient had previously accessed treatment. Concurrent substance use disorders are also collected, including but not limited to: crack cocaine, cannabis, alcohol, other illicit opioids, benzodiazepines, alcohol and other stimulants. As patient residential postcodes are

also collected by NDTMS, it is possible to link with the English Indices of Multiple Deprivation (IMD).

2.5.2 TREATMENT OUTCOMES PROFILE

The Treatment Outcomes Profile (TOP) was implemented across the English treatment system in October 2007 and is the national standard for reported in-treatment outcomes. The TOP is composed of 20 items that capture the frequency of use of opioids, crack cocaine, cocaine powder, amphetamines, cannabis, alcohol and one 'other' substance over the past 28 days. Also recorded are: injecting behaviour; the client's subjective ratings of physical health, psychological health, and quality of life; and the client's reports of criminal behaviours and indicators of social functioning. The TOP has shown excellent test-retest reliability for heroin use $\kappa=0.79$ and heroin abstinence $\kappa=0.88$ (Marsden et al., 2008). The TOP is designed to help review clients' progress towards attaining personal treatment goals. These core data are reported to NDTMS at the start of treatment, every six months during treatment, and at discharge.

The date the TOP assessment is completed is also submitted to NDTMS. Responses on the TOP are taken to pertain to the 28-day period prior to this date. The date is overlaid on the treatment journey. A TOP assessment completed within 14-days of the first modality date in the treatment journey is considered the treatment start, or admission, assessment. Where multiple TOPs are submitted for an individual, in the case for example when a patient accesses two treatment providers, the first assessment is utilised. TOPs subsequently submitted throughout the treatment journey are allocated into 6-month slots and where multiple TOPs are submitted within a given slot the latest assessment is utilised. At the end of treatment, signified by the discharge date of the final open modality, the latest TOP completed within +/- 14-days of this date is considered the discharge TOP.

2.5.3 TREATMENT INTERVENTIONS

NDTMS records how long patients are in receipt of pharmacological, psychosocial, in-patient detoxification and residential rehabilitation interventions. Pharmacological interventions usually involve a daily dose of an oral opioid agonist (i.e. methadone), a partial agonist (i.e. buprenorphine) or sometimes an antagonist (i.e. naltrexone). Patients are supported by a keyworker throughout the pharmacological intervention. Psychosocial interventions are also recommended, and are usually available from a specialist provider, which are often, but not always, available at the same service providing the pharmacological intervention. Psychosocial interventions can include contingency management, behavioural couples therapy, and cognitive-behavioural therapies. In-patient detoxification is sometimes required before a patient can engage in community-based treatment. Residential rehabilitation is generally a high-cost and low-volume intervention, reserved primarily for the most complex of cases.

2.5.4 DISCHARGE STATUS

When a patient is discharged from treatment, one of the following exit reasons are recorded: successful completion; drop-out (patient left treatment without discussion or before completing their care plan); unsuccessful transfer (patient was referred to another treatment service but did not enter treatment within 21 days); incarceration (treatment is prematurely terminated due to criminal justice action); or patient died. After this point, further treatment is classified as a new treatment journey.

2.5.5 OUTCOME MEASURE

The outcome measure used in all three studies was a composite measure of treatment effectiveness combining 'successful completion' and 'no re-presentation' (SCNR). In Study 1, the 'successful completion' component was measured within five years of patients initiating their index treatment journey. In Study 2 and Study 3, where clients were by definition already in treatment at the five-year mark, the 'successful

completion' component was measured in Year 6 and Year 7. Successful completion is defined as a clinician-verified report of a patient who had completed OST, was in remission from OUD, was abstinent from heroin and crack cocaine, and had achieved their care plan goals. The 'no re-presentation' component captures the extent to which this remission from OUD is enduring. In each study, I conducted a linkage with NDTMS six months following the discharge date to identify and remove patients from the composite treatment effectiveness criterion if they had re-presented to treatment within this timeframe. In Study 2 and 3, I was able to enhance this method by conducting a further linkage with prison-based treatment and the drug-related poisoning database to also remove patients from the treatment effectiveness criterion if they have been incarcerated or succumbed to fatal overdose in the six month period following discharge.

2.6 DATA STRUCTURE

There is a hierarchical, or multi-level, structure to the data captured by NDTMS.

Patients access treatment from a local provider in their area. Outcomes for patients from a given treatment provider are likely to be correlated as the same clinicians deliver similar treatment interventions to each of their patients. As such, patients are said to be 'nested' within the treatment provider. Further, each treatment provider is also 'nested' within a local administrative area responsible for the commissioning and delivery of drug treatment. As each local commissioner will set their own delivery targets for the treatment providers, this may influence the strategic decision making of providers in the local area, which may also lead to a correlation of outcomes among local providers. Failure to account for the hierarchical structure of the data can lead to biased estimates when modelling (Kahan and Morris, 2013), the results of which can misinform clinicians and policy-makers.

In Study 1, a total of 1,421 specialist treatment agencies submitted data on patients ($n=54,357$) initiating treatment in 2008/09 (median of 12 patients per service; interquartile range [IQR] 3–45) and there was a median of 302 patients per local treatment area (IQR 184–470). A three-level multivariable logistic regression was used to analyse the primary study outcome (i.e. patients nested in agencies, nested in local areas; see Section 2.6.4). In Study 2 and 3, however, the cohort was substantially reduced to less than 15% of the original cohort and there were too few patients at each treatment agency to incorporate this level in the modelling. As such, two-level (i.e. patients nested in local area) models were utilised to analyse the primary study outcome.

2.7 STATISTICAL ANALYSES

2.7.1 LATENT CLASS ANALYSIS

Latent Class Analysis (LCA) is a person-centred analytical approach that enables the researcher to identify sub-populations within cross-sectional data. LCA assesses the relationships between two or more discrete observed variables and clusters individuals together based on the similarity of their responses. In Study 1, LCA was utilised to identify patterns of poly-drug disorders from the concurrent substance use disorders which patients reported at the start of treatment. The substances included crack cocaine, cannabis, alcohol; non-medical opioids, stimulants (powder cocaine and *d*-amphetamine) and benzodiazepines. The potency of LCA lies in its ability to identify a relatively small set of sub-populations, which may differ in their response to treatment. With six concurrent substances under investigation, there are 64 possible combinations (i.e. $2^6 = 64$). This makes estimating the differential response to treatment difficult as there would be 2016 pairwise tests to perform (i.e. $(64 \times 63)/2 = 2016$). LCA substantially reduces this complexity by positing that there is an underlying (i.e. hidden or latent) categorical variable that divides people into mutually exclusive groups (i.e. classes).

The LCA was iterative with an unconditional 1-class model initially fit to the data and sequentially increased to a 6-class model. Each model used 5,000 random sets of starting values to guard against convergence on local maxima (McLachlan and Peel, 2000) and a minimum class size of 5% of the cohort was set for utility (Willey et al., 2016a; Borders and Booth, 2012). Class identification was informed by posterior fit statistics, including the Bayesian and Akaike information criteria and entropy. Patients can be fractionally assigned to multiple classes. For example, in a three class solution, there may be a 90% probability a patient belongs to Class A, a 7% probability they belong to Class B and a 3% chance of belonging to Class C. In Study 1, I assigned patients to their most probable class.

2.7.2 LATENT CLASS GROWTH ANALYSIS

Previously, I have used the reliable change index (Jacobson and Truax, 1991) to identify sub-populations of patients as they progress through treatment across two time periods, classifying patients into abstinent, improved, deteriorated or unchanged (Marsden et al., 2011). With 11 time periods available in Study 2 and Study 3, however, the reliable change index method is not a sustainable approach as there are more than a million potential combinations (i.e. $4^{10} = 1,048,576$).

Latent Class Growth Analysis (LCGA) is another person-centred approach and is appropriate for identifying a limited set of sub-populations from longitudinal data, particularly when there is anticipated heterogeneity in response over time (Grella and Lovinger, 2011; Hser et al., 2008a; Teesson et al., 2017b). LCGA has been utilised in several substance use studies, including: cocaine (Borders and Booth, 2012); methamphetamine (Brecht et al., 2008); cannabis (Caldeira et al., 2012); alcohol (Delucchi et al., 2004), and tobacco (Klein et al., 2013).

In Study 2, LCGA was used to empirically identify discrete, non-overlapping developmental trajectories of opioid use over a five-year period. In Study 3, the same LCGA approach was utilised to identify discrete, non-overlapping developmental trajectories for alcohol, crack cocaine, cannabis and the 'other' substance recorded on the TOP. As the prevalence of cocaine power and amphetamines never exceeded 5% across the five-year observational period, I did not apply LCGA to these substances.

A three-step procedure has been recommended (Nagin, 2005) to prevent trajectory group membership being influenced by both the covariates set and the distal outcome (Huang et al., 2010). In this approach, the identification and assignment of classes stems from an unconditional model (i.e. one without covariates and outcome) based on reported opioid use over the five-year in-treatment period.

LCGA is highly flexible. The method allows for latent intercept, latent slope, latent quadratic and higher latent terms (i.e. cubic etc) to be incorporated into the model. Because a model with a latent intercept only would imply zero change over time, I began by applying a latent intercept and a latent slope to the data using a single class solution (i.e. all patients belong to the same trajectory group). This model is capable of determining whether drug use increases or decreases over time, or if there is no reliable change. A further model was then generated including a latent quadratic term, allowing me to determine whether change is accelerating or decelerating over time. I used the Bayesian and Akaike information criteria to inform whether the inclusion of a latent quadric term improved model fit, and judged that incorporation of a latent quadratic term improved the models but that adding higher latent terms would add unnecessary complexity to the modelling process.

An iterative process was then implemented in which the number of classes fit to the data were sequentially increased up to a 6-class model. Each model assumed a Poisson distribution to model the count of heroin-using days and used 5,000 random sets of starting values to guard against convergence on local maxima (McLachlan and Peel, 2000). A minimum class size of 5% of the cohort was set for utility (Borders and Booth, 2012; Willey et al., 2016). Trajectory identification was informed by posterior fit statistics, including the Bayesian and Akaike information criteria and entropy. As patients are nested within different local treatment systems, a multi-level LCGA model was fitted, and intra-class correlation for each class was computed (Asparouhov and Muthén, 2007). As in the LCA approach, patients were assigned to their most probable trajectory class.

2.7.3 MULTINOMIAL LOGISTIC REGRESSION

A multinomial logistic regression was used to characterise the latent classes from both the LCA (Study 1) and LCGA (Study 2 and Study 3) approaches on the patient-level characteristics (STATA command: *mlogit*). Given the hierarchical structure of the study, with patients clustered in treatment services and services clustered in local treatment systems, confidence intervals (CI) were calculated using robust standard errors. Multinomial logistic regressions produce the relative risk ratio (RRR). The RRR is an estimate of how the risk of belonging to one class, relative to a referent class, is affected by patient-level characteristics.

2.7.4 MULTILEVEL LOGISTIC REGRESSION

A multilevel, multivariable logistic regression was utilised to estimate the likelihood of SCNR (STATA command: *meqrlogit*). In Study 1, the intraclass correlation (ICC) was used to assess intercept variation at the levels of treatment agency and local treatment area. In Study 2 and Study 3, the ICC was calculated for the local treatment area only (see section 2.6).

In all studies, a combination of variable-centred and person-centred covariates were used. In Study 1, together with the variable-centred covariates outlined in section 2.4.1, the person-centred drug use sub-populations derived from the LCA analysis were also included. In Study 2, I added to the set of covariates by including the heroin use developmental trajectories derived from the LCGA analysis. I also included a set of adjunctive treatment exposure measures; i.e. whether or not, alongside OST, patients had been exposed to psychosocial, in-patient detoxification or residential rehabilitation interventions. In Study 3, I ran separate analyses for each of the heroin developmental trajectory groups and added the alcohol, crack cocaine, cannabis and 'other drug' developmental trajectory groups to the above covariate set.

2.7.5 MISSING DATA

Both LCA and LCGA implement a full information maximisation likelihood approach. As a result, a patient with at least one assessment of substance use can be assigned to a latent class describing their longitudinal patterns of substance use. Analyses following LCGA are, however, likely to be impacted by the extent of missing data in the baseline predictors in a given model. Because a complete case analysis is likely to induce bias and risks reducing the precision of estimates (with no evidence that either the predictors or outcome variables were not missing-at-random (Little and Little, 2002)), a multiply imputed dataset was created for subsequent analyses (STATA procedure *MI impute chained*). Logistic regression, multinomial regression and predictive mean matching were utilised, respectively, for binary, multinomial or continuous covariates with missing data. Twenty probabilistic datasets were imputed and combined in analyses using Rubin's rules, resulting in a relative efficiency of over 98% (Rubin, 1987) and a reduction in power of than 1% (Graham et al., 2007).

2.8 SOFTWARE USED IN THIS THESIS

SPSS version 21 was used for data management of the NDTMS extract. STATA version 13.1 and 15.1 were utilised for multinomial logistic regressions and logistic regressions. MPlus version 7 was used for running the LCA and LCGA models.

Chapter 3 STUDY 1: EFFECTIVENESS OF TREATMENT FOR OPIOID USE DISORDER: A NATIONAL, FIVE-YEAR, PROSPECTIVE, OBSERVATIONAL STUDY IN ENGLAND

3.1 DESCRIPTION OF STUDY IN THE CONTEXT OF THE THESIS

This chapter presents a five-year investigation into the effectiveness of treatment in a national cohort of patients accessing treatment for OUD in England. NTORS (Section 1.3.2.4) was the last five-year, national cohort, study of patients accessing drug treatment services in England. The present study investigates the population of OUD patients initiating treatment in 2008/09, utilises Latent Class Analysis (Section 2.6.1) to identify sub-populations of OUD patients at treatment admission, and estimates the association between sub-population membership on an objective summative measure of treatment effectiveness: successful completion and non-representation.

This study was published as follows:

Eastwood, B., Strang, J., Marsden, J., 2017. Effectiveness of treatment for opioid use disorder: A national, five-year, prospective, observational study in England. *Drug and Alcohol Dependence* 176, 139–147.
<https://doi.org/10.1016/j.drugalcdep.2017.03.013>

3.2 ABSTRACT

BACKGROUND: This the first 5-year effectiveness study of publicly funded treatment for opioid use disorder (OUD) in England.

METHODS: All adults initiating treatment in 2008/09 in all 149 local treatment systems reporting to the National Drug Treatment Monitoring System (n=54,347). Admission polydrug use sub-populations were identified by Latent Class Analysis. The treatment outcome measure was 'successful completion and no re-presentation within six months' (SCNR) analysed by multilevel, multivariable logistic regression and funnel plots to contrast outcome by treatment system.

RESULTS: SCNR was achieved by 21.9%. Heroin and crack cocaine users were significantly less likely to achieve this outcome than patients who used heroin only (adjusted odds ratio [AOR] 0.90; 95% confidence interval [CI] 0.85-0.95). Older patients (AOR 1.09; CI 1.07-1.11), those employed (AOR 1.27; CI 1.18-1.37) and those enrolled for longer treatment were more likely to achieve the outcome measure. After risk adjustment, the local treatment systems that achieved substantially better outcome performance (14/149) had a lower rate of opiate prevalence in the local population at time of study initiation (incidence rate difference [IRD] 4.1; CI 4.0-4.2), fewer criminal offences per thousand (IRD 28.5; CI 28.1-28.8) and lower drug-related deaths per million (IRD 5.9; CI 5.9-5.9).

CONCLUSIONS: In an English national study, one fifth of patients successful completed treatment for OUD and did not present for further treatment within six months. Longer time in treatment increases the probability of achieving and maintaining clinical benefit from treatment. After risk-adjustment, an important minority of treatment systems achieve substantially better outcome performance.

3.3 INTRODUCTION

Heroin and non-medical opioids are associated with a substantial global burden of disease (Degenhardt et al., 2013). In the United States (US), it is estimated that 2.6 people per 1,000 aged 12 and above used heroin in the past year (Jones et al., 2015). In Europe, the estimated annual heroin use prevalence is 4 per 1,000 aged 15-64 (EMCDDA, 2015) and 7.3 per 1,000 among people aged 16-64 in England (Hay et al., 2014).

Opioid use disorder (OUD), and the conceptually identical 'opioid dependence', is a debilitating and often chronic bio-behavioural disorder (DSM-5; American Psychiatric Association, 2013; ICD-10; WHO, 2016). People with OUD typically use illicit heroin and/or non-medical opioid pharmaceutical products, developing physiologically dependence and strong motivational urges. Around one quarter of opioid users develop OUD (Gable, 1993; Anthony et al., 1994). Left untreated, OUD typically follows a chronic course causing substantial health, social and economic problems (Hser et al., 2001; Grella and Lovinger, 2011; Hser et al., 2015). In the classic Grella and Lovinger study, half of the sample died and a quarter did not experience any sustained improvement in their drug use (Grella and Lovinger, 2011).

The OUD population is far from homogenous. Several behaviours are associated with increasing severity of the disorder (Marsden et al., 2014) and treatment effectiveness may vary between sub-populations. For example, drop-out is more likely among patients with comorbid psychiatric conditions and more criminal justice involvement in the year before treatment, and less likely among those living with dependent children (Evans et al., 2009). Ethnic minority populations have been reported to have a lower rate of treatment episode completion (Mennis and Stahler, 2016). An important sub-population are polydrug users, typically involving concurrent use of one or more of the

following: alcohol, cocaine powder, smokeable (*crack*) cocaine and benzodiazepines (Darke and Hall, 1995; Monga et al., 2007; Harrell et al., 2012; Kuramoto et al., 2011). Heroin smokers who use crack cocaine are substantially less likely to be infected with Hepatitis C virus than those who inject heroin (Harrell et al., 2012). Opioid-polydrug users have been observed to have greater health and social problems (Leri et al., 2003b) and a relatively poorer response to OUD treatment (Williamson et al., 2006; Marsden et al., 2011, 2009).

The majority of countries with a high prevalence of OUD have an array of well-developed treatment services. The opioid medications methadone and buprenorphine are front-line, randomised-controlled trial supported pharmacotherapies (Mattick et al., 2014, 2009). In England, some OUD patients may receive psychosocial interventions without opioid psychotherapy. Interventions are typically provided by specialist community, primary care and hospital providers. Inpatient withdrawal management and drug-free residential rehabilitation services are also available (Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group, 2017). In addition to case management, national clinical guidelines recommend psychosocial interventions to address cognitive and behavioural symptoms of OUD (e.g. National Institute for Clinical Excellence, 2007).

Internationally, there have been several longitudinal cohort studies of the effectiveness of these interventions as delivered under routine conditions by US, Australian and English public treatment systems (e.g. Simpson and Sells, 1990; Stewart et al., 2002; Darke et al., 2007; Marsden et al., 2009; White et al., 2015). Taken together, these studies conclude that treatment is associated with reduced opioid use, drug injecting, and offending behaviour, and improvements in health (including a substantially reduced risk of fatal overdose), social functioning and employment.

Longitudinal cohort studies are time consuming and expensive. Public accountability means that the commissioners of publicly funded services need information on the effectiveness of treatment as it is delivered. Various proxy measures of outcome have been used in treatment systems research, including unsanctioned discharge (drop-out) from treatment and retention (Brorson et al., 2013; Stark, 1992; Faggiano et al., 2003). A commonly used measure is the proportion of patients treated who complete treatment successfully (Alterman et al., 2001). This indicator is associated with reduced drug use (Evans et al., 2009; Kornør and Waal, 2005), increased employment (Lang and Belenko, 2000; Zarkin et al., 2002; Evans et al., 2009; Sung and Chu, 2011), lower arrests and incarceration (Campbell et al., 2007; Evans et al., 2009; Gifford et al., 2014), and a reduced likelihood of readmission to treatment services (Luchansky et al., 2000). In the US, substantial inter-state (Arndt et al., 2013) and regional variation in completion rates have been reported (Hawkins et al., 2014), and this is now monitored at the federal/government level (Stahler et al., 2016).

The 'successful completion' indicator has a key limitation – it does not capture the extent to which treatment benefit is enduring. This is important because relapse is common, affecting 50-60% of people within six months after leaving treatment (McLellan et al., 2005). The process of achieving stable recovery from OUD may involve several cycles of treatment over a decade or more (Dennis et al., 2005; Hser et al., 1997).

To fully assess the effectiveness of treatment systems, national administrative databases need to be able to capture this process, yet the requirements of such systems are difficult to implement. In the US, the absence of a patient consent prevents linkage across consecutive treatment episodes. At the national level, the impact of this is twofold: it is not possible to objectively assess whether an individual has previously

engaged in treatment (an indicator of patient-level complexity (Marsden et al., 2012b; Siguel and Spillane, 1978). It is also not possible to determine whether a patient's successful completion status is enduring.

England has a well-developed public treatment system for drug use disorders with service delivery involving specialist clinics in the National Health Service (NHS) and non-governmental sector. Services are commissioned by 149 local treatment systems across the country aligned to local government geographical boundaries. All public providers report clinical and effectiveness data to the National Drug Treatment Monitoring System (NDTMS). NDTMS is operated by Public Health England and provides outcome monitoring and performance benchmarking for each local system (see Marsden et al., 2009 for an operational description). The latest national report shows that 28% of people treated for OUD complete treatment successfully (Public Health England, 2016a).

With temporal linkage of episodes, NDTMS can record re-presentation to treatment as a proxy remission indicator. To our knowledge, a 'successful completion and no re-representation' outcome measure has not been used in previous OUD treatment systems research. Accordingly, the aim of this study was to estimate the effectiveness of OUD treatment in England for OUD using this indicator and contrast the effectiveness of local treatment systems.

3.4 METHODS

3.4.1 DESIGN

This was an English national, five-year, prospective, observational cohort study of publicly-funded, specialist treatment services for OUD reporting to the NDTMS, and reported following the STROBE guideline for observational research (Elm et al., 2007).

The population for the study was all adults (≥ 18 years) diagnosed with OUD who presented for treatment in England between 1 April 2008 and 31 March 2009.

The study included all local treatment systems and all operational specialist community agencies in the NHS and third-sector providing pharmacotherapies, psychosocial interventions and adjunctive support services for OUD in community, inpatient (short-term medically supervised withdrawal), and residential (drug-free rehabilitation) settings.

3.4.2 OUD TREATMENTS

The opioid pharmacotherapies included methadone, buprenorphine and also naltrexone. Psychosocial interventions such as contingency management and motivational interviewing complement pharmacotherapy and target underlying psychological aspects of dependence. In addition to opioid pharmacotherapy and/or psychosocial interventions, a patient's treatment programme could include adjunctive 'recovery support' services, including: facilitated access to mutual aid; complementary therapies; and family, housing, employment, education and training supports.

3.4.3 TREATMENT EPISODES AND JOURNEYS

Following the NDTMS reporting protocol, each patient-level 'treatment journey' comprised: a single episode of pharmacotherapy or psychosocial intervention provided by a clinic; enrolment in concurrently delivered medication and psychosocial interventions (from one or more clinics); or a continuing care package in which an intervention was followed by one or more further interventions. Episodes commencing after 21 days are classified as a new treatment journey (Public Health England, 2015a). Recovery support services are offered concurrently or following a treatment episode. Patients are regularly reviewed, treatment provision changes, and at the end

of the ‘treatment journey’, patients who overcome their dependence are successfully discharged from the treatment system.

When a patient was discharged from treatment, one of the following exit reasons was recorded: successful completion; drop-out (patient left treatment without discussion or before completing their care plan); unsuccessful transfer (patient was referred to another treatment service but does not enter treatment within 21 days); incarceration (treatment is prematurely terminated due to criminal justice action); or patient died. After this point, further treatment was classified as a new treatment journey.

3.4.4 OUTCOME MEASURE

The outcome measure for the study combined two components: successful completion and no re-presentation. Successful completion was assigned to each patient that was reported by the clinic as meeting the following criteria within five years (ending 31 March 2014):

- in remission from OUD;
- abstinent from all opioids and crack cocaine;
- completed all opioid pharmacotherapy and psychosocial interventions;
- met all care plan goals, with mutual agreement to exit treatment.

For the ‘no re-presentation’ element of the outcome measure, we judged that a six-month period was reasonable (ending 30 September 2014). Therefore, the effectiveness measure was assigned to those patients who met the above criteria at exit from treatment and did not re-present for any treatment within six months (‘successful completion, no re-representation’, SCNR for economy herein).

3.4.5 COVARIATES

We followed an integrated variable-centred and person-centred approach to evaluate treatment effectiveness for OUD using the following patient demographic, clinical information and previous treatment exposure (all recorded at initial assessment):

Demographic. Sex; age (centred at 18 years and grouped in five-year increments); Black and Minority Ethnicities (BME: a legal monitoring requirement (*Race Relations (Amendment) Act, 2000*)); employed; housing problems (defined primarily as having no fixed abode, but can also include squatting, short-term hostel/B&B, staying with friends/relatives; [(homeless, herein)]).

Social deprivation. Local area deprivation was measured by the Indices of Multiple Deprivation (IMD; Department for Communities and Local Government, 2007). IMD data were linked to NDTMS based on the patient's residential postcode district or the location of their first treatment provider in instances of missing postcode information. As opposed to poverty, which indicates a lack of financial resources to meet a person's needs, deprivation is a term that indicates a lack of resources across multiple domains, not just income (Ministry of Housing, Communities and Local Government, 2019). It is important to adjust for deprivation as it has been shown to be strongly associated with numerous outcomes in the OUD population including, for example, an increased risk of non-fatal overdose and longer prison sentences (Carrà et al., 2017) and a decreased likelihood of achieving abstinence from illicit heroin during specialist treatment (Marsden et al., 2012b). In the wider community, it is interesting to note that there is also an association between the level of deprivation and the rate at which General Practitioners prescribe anti-depressants, benzodiazepines, gabapentinoids, z-drugs and opioids (Marsden et al., 2019b).

The IMD used in this study is a summary measure of 37 distinct resource indicators covering income, employment, health and disability, education, housing, local environment and crime. The IMD is a relative measure of deprivation, meaning that while it can be used to indicate that a patient is from a more deprived area than another patient, it cannot be used, for example, to say that the former is twice as deprived as the latter. Deprivation has been estimated at a local level in England since the 1970s, and the 2007 estimates are generated for each of the 32,482 Lower Super Output Areas (LSOA) in England at the time (Department for Communities and Local Government, 2007). LSOAs are geographical areas in which 1,000 to 3,000 persons are resident. All postcodes within a given LSOA have been assigned the same deprivation value. It is important to note that the IMD measure provides only an insight into deprivation within a given LSOA, which is to say that many deprived people are resident in non-deprived areas and vice versa. Accurately capturing person-level deprivation is, however, beyond the scope of a national administrative database and the IMD is considered to provide a reasonable proxy of individual-level deprivation.

Injecting status. Three levels of injecting status are recorded at the start of treatment: never injected; lifetime history of injecting, and current injector.

Career length. The number of years between first initiating opioid use and enrolment in the index treatment journey (length of the substance-using career). This measure was mean centred and coded in five-year increments.

Treatment history. Referral route into treatment was categorised into whether the patient was self-referred, referred via the criminal-justice system or other (e.g., referral from health service or substance abuse service). Whether an individual had previously accessed treatment was also included.

3.4.6 DRUG USE SUB-POPULATIONS

Given anticipated heterogeneity in drug use profile of the OUD population at presentation to treatment (Monga et al., 2007; Public Health England, 2016a), we used latent class analysis (LCA [Section 3.1]) in Mplus to identify discrete sub-populations of OUD patients who presented for treatment with concurrent disorder with one or more of the following 6 substances: crack cocaine; cannabis; alcohol; non-medical opioids; stimulants (powder cocaine and *d*-amphetamine) and benzodiazepines.

The LCA was iterative with an unconditional 1-class model initially fit to the data and sequentially increased to a 6-class model. Each model used 5,000 random sets of starting values to guard against convergence on local maxima (McLachlan and Peel, 2000) and a minimum class size of 5% of the cohort was set for utility (Willey et al., 2016a; Borders and Booth, 2012). Class identification was informed by posterior fit statistics, including the Bayesian and Akaike information criteria and entropy. A multinomial logistic regression was then used to characterise the latent classes on the patient-level characteristics. Given the hierarchical structure of the study, with patients clustered in treatment services and services clustered in local treatment systems, confidence intervals (CI) were calculated using robust standard errors.

3.4.7 OUTCOME ANALYSIS

A three-level, multivariable logistic regression was used for the analysis of the outcome measure (Stata command: *meqrlogit*). The complete-case model contained the following random intercepts: patients (level one); treatment services (level two); and local treatment system (level three). Model discrimination and variation (at level two and three) was estimated by c-index (Hanley and McNeil, 1982), and intra-cluster correlation (ICC), respectively.

Reflecting the hierarchical design of the study (Hofmann, 1997; Heo and Leon, 2008) and with alpha, statistical power and a medium effect size on the outcome measure pre-set (0.05, 0.90 and $f^2 = 0.15$, respectively [Cohen, 1988]), we ensured that there were at least 15 cases per covariate in the regression analysis to minimise overfitting (Green, 1991; Babyak, 2004).

With no contrary evidence that data loss was missing-at-random (Little and Little, 2002), a multiply imputed dataset was computed by chained equations (Stata command: *mi: impute chained*). An all-case multivariate logistic model was run to check on potential bias and loss of precision (Sterne et al., 2009). To achieve a relative efficiency above 98% (Rubin, 1987), and to ensure that reduction in power was less than 1% (Graham et al., 2007), 20 datasets of probabilistic values were created, each analysed separately, and then combined using Rubin's rules.

3.4.8 ANALYSIS OF LOCAL TREATMENT SYSTEMS

A fixed-effects approach was used to determine the relative effectiveness of each local treatment system because random intercepts could mask real variation in achieving the outcome (Marsden et al., 2012b). For each treatment system, predicted outcome probabilities were summed across patients and divided by the number of patients treated in the area. A risk-adjusted outcome rate was then calculated by dividing the expected rate by the observed rate and multiplying this by the national average.

A funnel plot with 95% control limits (Spiegelhalter, 2005) then identified areas where outcome performance was better or worse than expected (where the area was located above or the control limit, respectively). Local treatment systems rates of opiate prevalence, offending and drug-related deaths were contrasted by incidence-rate ratio.

Outcome performance was contrasted using pooled estimates of the rate of opiate users per thousand inhabitants (Hay et al., 2010), incidence of drug related deaths per million inhabitants (Public Health England, 2016b) and the criminal offence rate per thousand inhabitants (Office for National Statistics, 2016) The offending rate was based on the local area population estimates used in the development of the opiate prevalence estimates (Hay et al., 2010).

3.5 RESULTS

3.5.1 STUDY COHORT AND FOLLOW-UP

The population for the study was all adults (≥ 18 years) diagnosed with OUD who presented for treatment in England between 1 April 2008 and 31 March 2009 (N=56,156). As 1,799 (3.2%) people did not commence treatment by 31 March 2014, they were removed from further analyses.

Patients in the cohort ($n = 54,357$) commenced treatment for OUD in 1,421 specialist clinics and primary care teams in the National Health Service (NHS) and the non-governmental sector (median of 12 patients per service; IQR 3-45), and in all 149 local treatment systems in England (median 302 patients per area; interquartile range [IQR] 184-470)].

At the end of the five-year period, 7,890 people (14.5%) were continuously enrolled in treatment for OUD. Given the aims of the present study, this group was removed. Among the final all-case cohort ($n = 46,467$), 9,007 patients (19.4%) had missing observations on one or more covariates, yielding a complete-case cohort of 37,460. The covariate with the highest level of missing data was length of heroin use career (11.4%), followed by employment status (9.1%), housing status (3.4%) and injecting (3.4%).

3.5.2 DRUG USE SUB-POPULATIONS

At clinical assessment, 67% of patients had a concurrent substance use disorder, as follows: crack cocaine (44.1%), cannabis (14.1%), alcohol (13.3%), other illicit opioids (11.4%), benzodiazepines (9.4%) and other stimulants (8.8%).

Table 4.1 displays the results of the LCA models. The value of each information criterion (Akaike, Bayesian and adjusted Bayesian) reduced as the number of classes increased, indicating successively better fitting models. The bootstrapped likelihood ratio test confirmed that each model was a statistically better fit than the preceding one. Entropy was high (>0.8) for all except the 3-class solution, which reflected relative uncertainty in the assignment of individuals to the third class. The 5-class and 6-class solutions resulted, however, in at least one class with less 5% of the cohort. Accordingly, we judged that a 4-class solution best identified the heroin and other drug use sub-populations at treatment admission, and labelled these as follows:

- **Class 1** (n=30,339, 56%: *heroin low level concurrent drug use disorders*);
- **Class 2** (n=2,794, 5%: *heroin, crack, alcohol*);
- **Class 3** (n=17,907, 33%: *heroin, crack*);
- **Class 4** (n=3,257, 6%: *heroin, crack, cannabis*).

Table 3.1 Unconditional latent class analysis of drug use at presentation to treatment (n=54,347)

Model ^a							
Parameter	Class 1		Class 2	Class 3	Class 4	Class 5	Class 6
No. of parameters	6		13	20	27	34	41
AIC	266,371.29		264,740.91	262,525.26	261,201.63	260,527.17	260,033.40
BIC	266,424.71		264,856.65	262,703.32	261,442.02	260,829.88	260,398.43
aBIC	266,405.65		264,815.33	262,639.76	261,356.22	260,721.83	260,268.13
aBIC change (%)	-		-0.60	-0.82	-0.49	-0.24	-0.17
Entropy	-		0.999	0.718	0.830	0.861	0.857
BLRT	-		-133,179.65	-132,357.45	-131,242.63	-130,573.82	-130,229.58
BLRT reduction (%)	-		-	0.62	0.84	0.51	0.26
Class (probability)							
	1	1.00 (1.00)	0.44 (1.00)	0.06 (0.99)	0.56 (0.83)	0.29 (0.99)	0.01 (0.71)
	2	-	0.56 (1.00)	0.38 (1.00)	0.05 (0.99)	0.04 (0.97)	0.55 (0.79)
	3	-	-	0.56 (0.69)	0.33 (0.99)	0.05 (0.99)	0.04 (0.99)
	4	-	-	-	0.06 (0.99)	0.06 (0.99)	0.06 (0.99)
	5	-	-	-	-	0.56 (0.84)	0.29 (0.99)
	6	-	-	-	-	-	0.05 (0.98)

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion;

aBIC, sample-size adjusted BIC; BLRT, bootstrapped likelihood ratio test (all $P < 0.00005$).

^a For the following drugs: crack cocaine, cannabis, alcohol, other opioids, benzodiazepines and other stimulants.

Classification based on most likely latent class membership.

3.5.3 CHARACTERISTICS OF THE COHORT

Table 3.2 shows the demographic and clinical characteristics of the cohort and the results of the multinomial logistic regression analysis of the profile of the drug problem classes on socio-demographic, injecting, heroin career and treatment referral characteristics (with the heroin and low concurrent drug use disorders [class 1] as the referent).

There were relatively less employment and more homelessness among the members of classes 2, 3 and 4. Class 4 was also relatively more likely to be referred to treatment from the criminal justice system (35.3%) and have previous OUD treatment (50.4%).

3.5.4 TREATMENT EXPOSURE AND STATUS AT EXIT

Patients in the cohort received a median of 31.0 weeks of treatment (IQR 12.6-80.3) and 13,360 (28.8%) successfully completed their treatment journey (**Table 3.3**). One-third (32.1%) of discharged patients were readmitted for further treatment for substance use disorders within six months.

Readmission was more likely for those who were incarcerated (re-admission rate 45.2%; odds ratio [OR] 2.67; 95% CI 2.50-2.82), dropped out (re-admission rate 34.8%; OR 1.72; 95% CI 1.63-1.81), or transferred unsuccessfully to another SUD treatment service (re-admission rate 28.3%; OR 1.27; 95% CI 1.20-1.35) compared with those who completed treatment successfully (re-admission rate 23.7%).

Relative to Class 1, patients assigned to Class 2 and Class 4 were less likely to have received opioid pharmacotherapy, Class 4 was more likely to have received psychosocial interventions, and Class 2 received more in-patient services. Class 1 received the least amount of residential services and was retained in treatment longer

than any other class. Class 3 reported more incarceration, unsuccessful transfers and dropouts, but less deaths, while Class 2 had fewer incarcerations but more drop outs. There were relatively fewer deaths in Class 4.

3.5.5 SUCCESSFUL COMPLETION OF TREATMENT AND NO RE-PRESENTATION WITHIN SIX MONTHS

Overall, 21.9% of the cohort (10,194) attained the SCNR outcome (**Table 3.3**). Class 3 were less likely to achieve the outcome. After negative multi-collinearity screening for all covariates, the results of the unadjusted, covariate adjusted complete-case (n=37,460) and multiply-imputed, all-case (n=46,467) analyses are shown in **Table 3.4**.

The complete- and all-case models yielded very similar covariate estimates. In the all-case model, with statistically significant adjustment for clustering effects associated with treatment agency and local treatment system (ICC 0.13 and 0.17, respectively) there was satisfactory discrimination between patients who achieved the SCNR outcome (c-index 0.74; 95% CI 0.74-0.75).

There was an increased likelihood of positive outcome among older patients, those with pre-treatment employment, and those who with longer time enrolled in treatment (particularly for more than 2 years; adjusted odds ratio [AOR] 2.60; 95% CI 2.43-2.78).

A negative outcome was associated with men, patients who were homeless before admission and in areas of greater social deprivation (gradient with likelihood lowest at highest quintile; AOR 0.77; 95% CI 0.70-0.85); drug injectors; those referred from the criminal justice system; those with previous treatment for OUD; those with shorter heroin using career; and members of class 3.

Table 3.2 Characteristics of the cohort and drug use sub-populations

Covariate	Total		Class 1 n=30,339	Class 2 n=2,794	Class 3 n=17,907	Class 4 n=3,257
	n	(%)				
Socio-demographic						
Male	41,099	(75.6)	(76.5)	(74.9)	(73.0)	(82.0)
Age ^a	32.9	(7.8)	32.9 (7.9)	34.2 (7.9)	33.0 (7.5)	31.9 (7.9)
Black/Minority Ethnic	7,342	(13.5)	(10.9)	(15.8)	(15.9)	(22.4)
Employed	6,222	(12.5)	(14.7)	(8.1)	(9.7)	(11.4)
Homeless	17,343	(32.9)	(29.5)	(43.1)	(36.8)	(35.1)
Social deprivation:						
Quintile 1 (lowest)	10,857	(20.0)	(21.6)	(19.9)	(17.1)	(20.4)
2	10,922	(20.1)	(19.9)	(21.9)	(20.1)	(20.3)
3	10,823	(19.9)	(19.9)	(23.3)	(19.3)	(20.2)
4	10,859	(20.0)	(19.8)	(18.9)	(20.3)	(20.6)
Quintile 5 (highest)	10,896	(20.0)	(18.7)	(16.0)	(23.2)	(18.5)
Clinical						
Heroin career ^a	11.4	(7.5)	(7.6)	(8.3)	(7.2)	(7.4)
Drug injecting:						
Never	17,715	(33.6)	(32.8)	(32.5)	(33.1)	(44.5)
Lifetime	18,004	(34.2)	(34.9)	(35.4)	(33.5)	(30.4)
Current	16,996	(32.2)	(32.3)	(32.1)	(33.4)	(25.0)
Referral source:						
Other	17,453	(32.1)	(35.0)	(35.1)	(27.6)	(27.2)
Self	20,570	(37.8)	(39.4)	(37.6)	(35.2)	(37.5)
Criminal justice	16,334	(30.0)	(25.6)	(27.3)	(37.1)	(35.3)
Previous OUD treatment:	30,212	(55.6)	(55.6)	(52.4)	(57.0)	(50.4)
< 6 months	20,835	(38.3)	(35.3)	(45.1)	(41.4)	(44.1)
6 months to < 1 year	8,917	(16.4)	(16.1)	(16.4)	(16.9)	(17.0)
1 year to < 2 years	8,014	(14.7)	(15.4)	(14.3)	(13.6)	(14.9)
2 years to 5 years	16,591	(30.5)	(33.2)	(24.3)	(28.1)	(24.0)

Class 1: Heroin and low likelihood of problem substance use; **Class 2:** Heroin, problem crack cocaine and alcohol use;

Class 3: Heroin and crack cocaine use; **Class 4:** Heroin and crack and cannabis use.

Figures in parentheses in table are percentages unless otherwise stated.

^a Year (SD)

Emboldened percentages and means are statistically significant ($P < 0.05$) from multivariable, multinomial logistic regression (Class 1: referent).

Table 3.3 Treatment interventions received, by treatment leavers, SCNR outcome and latent class

		Class 1: <i>Heroin, low poly-substance</i>	Class 2: <i>Heroin, crack, alcohol</i>	Class 3: <i>Heroin, crack</i>	Class 4: <i>Heroin, crack, cannabis</i>
Treatment characteristics	Total (n=46,467)	(n=25,469)	(n=2,496)	(n=15,566)	(n=2,936)
Exposure – interventions received					
Opioid pharmacotherapy, n (%)	36,122 (77.7)	20,377 (80.0)	1,602 (64.2)	12,082 (77.6)	2,061 (70.2)
Psychosocial interventions, n (%)	25,742 (55.4)	13,682 (53.7)	1,537 (61.6)	8,694 (55.9)	1,829 (62.3)
In-patient withdrawal management, n (%)	3,010 (6.5)	1,546 (6.1)	275 (11.0)	1,021 (6.6)	168 (5.7)
Residential rehabilitation, n (%)	1,620 (3.5)	711 (2.8)	167 (6.7)	617 (4.0)	125 (4.3)
Total time in treatment journey					
Median weeks (IQR)*	31.0 (12.6-80.3)	34.3 (13.3-87.0)	25.6 (11.8-67.9)	28.0 (11.6-73.4)	27.0 (11.9-69.9)
Treatment exit status					
Successful completion, n (%)	13,360 (28.8)	7,675 (30.1)	718 (28.8)	4,066 (26.1)	901 (30.7)
Died, n (%)	684 (1.5)	435 (1.7)	52 (2.1)	182 (1.2)	15 (0.5)
Incarcerated, n (%)	7,425 (16.0)	3,820 (15.0)	299 (12.0)	2,845 (18.3)	461 (15.7)
Unsuccessful transfer, n (%)	8,385 (18.1)	4,498 (17.7)	449 (18.0)	2,922 (18.8)	516 (17.6)
Dropped out, n (%)	16,613 (35.8)	9,041 (35.5)	978 (39.2)	5,551 (35.7)	1,043 (35.5)
Treatment outcome					
Successful completion and no re-presentation within six months, n (%)	10,194 (21.9)	5,882 (23.1)	566 (22.7)	3,063 (19.7)	683 (23.3)

Table 3.4 Unadjusted and multi-level, complete-case and all-case multivariable logistic regression of SCNR outcome

	Unadjusted	Complete-case	All-cases
	OR (95% CI)	AOR (95% CI)	AOR (95% CI)
Covariates	(n=37,460)	(n=37,460)	(n=46,467)
<i>Socio-demographic</i>			
Male	0.87 (0.82, 0.92)	0.88 (0.83, 0.94)	0.88 (0.83, 0.93)
Age	1.07 (1.06, 1.09)	1.09 (1.07, 1.11)	1.09 (1.07, 1.11)
BME	1.11 (1.03, 1.20)	1.05 (0.97, 1.14)	1.02 (0.94, 1.09)
Employed	1.46 (1.36, 1.58)	1.24 (1.15, 1.34)	1.27 (1.18, 1.37)
No fixed abode	0.74 (0.70, 0.79)	0.85 (0.80, 0.91)	0.86 (0.81, 0.91)
Deprivation:			
Quintile 2	0.88 (0.80, 0.96)	0.93 (0.84, 1.02)	0.94 (0.86, 1.02)
Quintile 3	0.82 (0.74, 0.90)	0.91 (0.82, 1.00)	0.91 (0.83, 1.00)
Quintile 4	0.79 (0.71, 0.87)	0.84 (0.76, 0.93)	0.86 (0.78, 0.94)
Quintile 5 (highest)	0.63 (0.57, 0.70)	0.74 (0.67, 0.83)	0.77 (0.70, 0.85)
<i>Clinical</i>			
Injecting:			
Previously injected	0.81 (0.76, 0.86)	0.87 (0.81, 0.93)	0.86 (0.81, 0.91)
Currently injector	0.59 (0.55, 0.63)	0.64 (0.60, 0.69)	0.64 (0.60, 0.69)
Referral route:			
Self	0.95 (0.88, 1.01)	0.96 (0.90, 1.03)	0.97 (0.92, 1.04)
Criminal justice	0.58 (0.54, 0.63)	0.68 (0.63, 0.74)	0.68 (0.63, 0.73)
Drug use class:			
Class 2: Heroin, crack & alcohol	0.92 (0.81, 1.03)	1.02 (0.90, 1.15)	0.97 (0.87, 1.08)
Class 3: Heroin & crack	0.82 (0.77, 0.87)	0.92 (0.86, 0.98)	0.90 (0.85, 0.95)
Class 4: Heroin, crack & cannabis	0.99 (0.89, 1.11)	1.08 (0.97, 1.20)	1.02 (0.92, 1.12)
Previously treated	0.64 (0.61, 0.67)	0.66 (0.62, 0.69)	0.66 (0.63, 0.70)
Heroin career	0.99 (0.97, 1.00)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)
Time in index treatment journey:			
6 months to < 1 year	1.28 (1.19, 1.39)	1.28 (1.19, 1.38)	1.32 (1.23, 1.41)
1 year to < 2 years	1.43 (1.33, 1.55)	1.40 (1.29, 1.51)	1.39 (1.30, 1.49)
2 years to 5 years	2.70 (2.51, 2.90)	2.59 (2.41, 2.79)	2.60 (2.43, 2.78)
Model statistics			
Constant	-	0.38 (0.33, 0.43)	0.39 (0.34, 0.44)
Wald X ² (d.f. = 21)	-	1,538	1,834-1,854
LR test X ² (d.f. = 2)	-	938	1,342-1,349
Random effects parameters (ICC):			
Treatment system (Level 3)	-	0.01 (0.00, 0.02)	0.17 (0.11, 0.27)
Treatment agency (Level 2)	-	0.13 (0.11, 0.15)	0.13 (0.11, 0.15)

SCNR, 'successful completion of treatment journey and no representation to treatment within six months'; OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval; d.f., degrees of freedom; ICC, intra-class correlation coefficient. Emboldened percentages and means are statistically significant (P < 0.05)

3.5.6 COMPARISON OF LOCAL TREATMENT SYSTEMS

Following risk-adjustment, 14 of 149 local treatment systems were classified as achieving performance that was better than expected on the SCNR outcome, and 38 local treatment systems achieved performance that was worse than expected (**Figure 3.1**). In comparison to the better performing areas, these 38 areas were characterised with a higher estimated level of opiate use in the local population (an extra 4.1 (95% CI 4.0-4.2) opiate users per thousand population), a higher level of drug-related offences (an extra 28.5 (95% CI 28.1-28.8) offences per thousand population), and more drug-related deaths (an extra 5.9 (95% CI 5.9-5.9) deaths per thousand population) (**Table 5**).

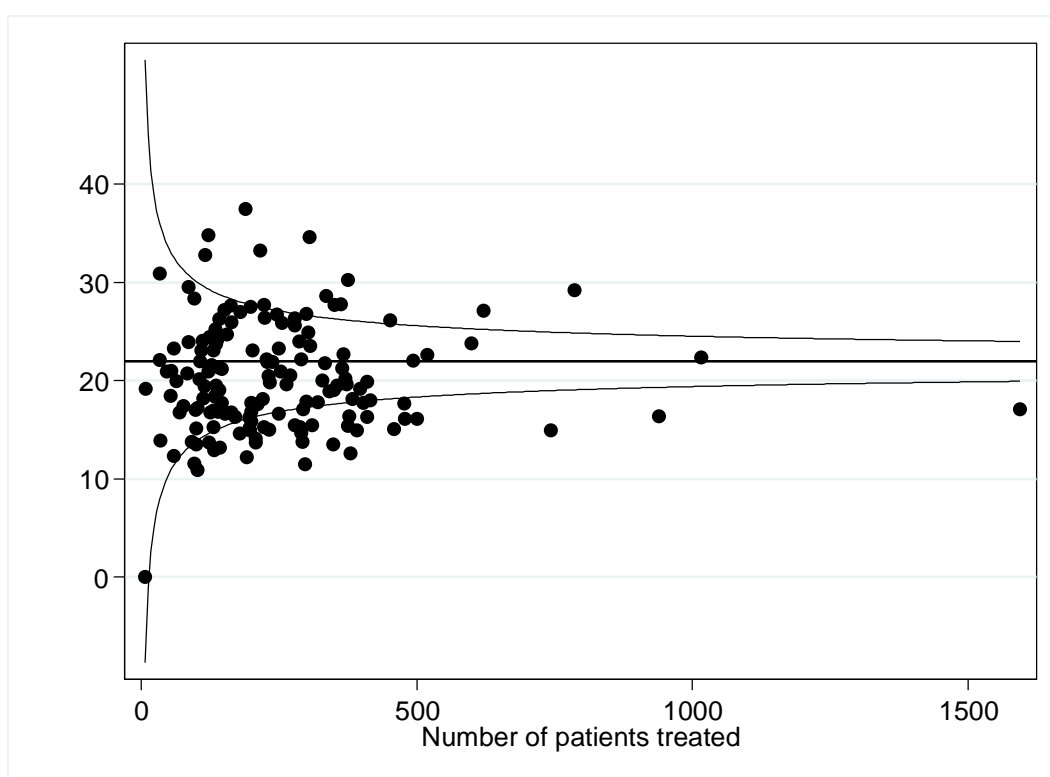


Figure 3.1 Funnel plot of outcome performance (SCNR rate) by local treatment system

NB: The horizontal line is the national average for the SCNR outcome. The curved lines are the upper and lower 95% confidence interval. Each black dot represents a local treatment system. Local systems lying above the upper CI have an SCNR outcome performance that is better than average after risk-adjustment. Local systems lying below the lower CI have an SCNR outcome performance that is worse than average after risk-adjustment.

Table 3.5 Population estimates by local treatment system outcome performance, England

Estimates	All local systems (n=149)	Performance better than expected (n=14)	Performance worse than expected (n=38)	Incidence rate difference
Size of population aged 16-64 ^a	172,000 (127,100-272,700)	210,550 (171,250-433,725)	170,100 (140,625-219,725)	-
Number of opiate users per 1,000 ^a	7.7 (6.5-9.0)	6.3 (5.0-7.6)	10.4 (9.1-11.9)	4.1 (4.0-4.2)
Offence rate per 1,000 ^b	106.3 (106.2-106.4)	97.5 (97.2-97.8)	126 (125.7-126.2)	28.5 (28.1-28.8)
Drug-related deaths per million ^c	33.5 (32.7-34.4)	32.9 (30.2-35.8)	38.8 (36.9-40.8)	5.9 (5.9-5.9)

Figures in parentheses are 95% confidence intervals

^a Median and inter-quartile range (Hay et al., 2010)

^b (Office for National Statistics, 2016)

^c (Public Health England, 2016b)

3.6 DISCUSSION

Over the five-year observation period, we observed that nearly one in three patients successfully completed treatment for OUD. Reinforcing previous research (Luchansky et al., 2000), patients who successfully completed treatment were least likely to be re-admitted to treatment within a subsequent six month period. In our national population of patients accessing publicly-funded treatment, one in five achieved a sustained benefit from treatment.

Other studies have noted two (Shand et al., 2011), three (Harrell et al., 2012; Monga et al., 2007), five (Kuramoto et al., 2011), or eight (Patra et al., 2009) latent class structures. Our analysis of polydrug dependence in patients seeking treatment for OUD in England revealed a four class structure. Crack cocaine was a defining characteristic in three of these classes, with one class being further classified with alcohol dependence and another classified with cannabis dependence. It is interesting to note that the only crack cocaine class without alcohol or cannabis dependence had worse outcomes than the heroin with low polydrug class.

3.6.1 INTEGRATION WITH THE LITERATURE

Unlike other large-scale studies on treatment completion (Arndt et al., 2013; Mennis and Stahler, 2016), in our unadjusted models patients from Black and Minority Ethnicities (BME) were more likely to recover. After controlling for other socio-economic factors, however, this disparity no longer held, highlighting the importance controlling for employment and stable housing (Saloner and Lê Cook, 2013; Hawkins et al., 2014). Our findings provide general support for the construct of 'physical capital' (Cloud and Granfield, 2008) playing a major role in recovery from heroin use disorder, as employment and stable housing were found to significantly affect the likelihood of

recovery. The finding that increased time spent engaged in treatment increases the likelihood of successful completion aligns with previous research (Hubbard et al., 2003; Simpson and Sells, 1990) and provides evidence that OUD treatment should not be time-limited (Advisory Council on the Misuse of Drugs, 2014).

After controlling for patient-level and area-level deprivation predictors of outcome, local treatment systems that were performing significantly below the expected rate also appeared to have a much larger opiate using population and, presumably as a result of this, a higher rate of both offending and drug-related deaths. We are not able to determine a mechanism for this association. There may be social network influences in operation. For example, social networks can influence both a transition to injecting heroin (Neaigus et al., 2006) and the decision to share injecting equipment (De et al., 2007). Heroin users who have achieved abstinence often cite moving away from drug-using social networks and receiving support from non-using friends as a contributory factor to their success (Best et al., 2008).

3.6.2 STRENGTHS AND LIMITATIONS

The main study strength is the national, large scale, long-term follow-up of all individuals accessing treatment for heroin use disorder in England and the utilisation of the national administrative database to monitor relapse. Unlike other comprehensive administrative datasets (Sahker et al., 2015; Alterman et al., 2001; Stahler et al., 2016), NDTMS has patient-level identifiers that enable cross-referencing with subsequent treatment admissions. This utility provides not only an objective summative measure of the sustainability of recovery in this population, it also enables national administrative systems to objectively capture whether patients had previously accessed treatment services, which is an important negative predictor of treatment outcome (Siguel and Spillane, 1978; Marsden et al., 2012b).

Several study limitations are also acknowledged: firstly, our analysis of OUD sub-populations is based on clients entering the treatment system in 2008/09. It is possible that since this period, with the rise of novel psychoactive substances for example, a different class structure would emerge for clients currently accessing treatment. Second, we were not able to access data from the national deaths registry or the national prisons system, and there remains a concern that at least some of our patients who did not re-present to treatment were simply unable to. Third, while all available covariates in NDTMS were screened in the present analysis, other covariates could further elucidate the likelihood of sustaining recovery, including treatment motivation (Simpson and Joe, 1993), engagement (Simpson et al., 1995) and other recovery strengths (Gossop et al., 2002d). Fourth, it is possible that other interventions were experienced by the patients in this cohort, such as privately-funded residential treatment or attending Alcoholics Anonymous, but these interventions are not captured by NDTMS and it is not possible to assess the potential impact these may have had.

3.6.3 CONCLUSIONS

Relapse requiring treatment is relatively common in the six months following treatment completion. This study highlights the importance of including re-presentation to treatment as a summative measure of the effectiveness of local treatment systems. We note a sizeable proportion of individuals, nearly one in seven, who have been continuously engaged in treatment throughout the five-year observation period. The next questions for our research group are whether, and to what degree, heroin and other drug use changes throughout this time period; how change in heroin use relates to change in other drugs; whether five-year in-treatment change predicts subsequent successful completion of treatment, and to examine the longitudinal inter-relationship between substance use, employment and housing.

Chapter 4 **STUDY 2: CONTINUOUS OPIOID SUBSTITUTION TREATMENT OVER FIVE YEARS: HEROIN USE TRAJECTORIES AND OUTCOMES**

4.1 DESCRIPTION OF STUDY IN THE CONTEXT OF THE THESIS

In the previous chapter, we demonstrated that latent polydrug subpopulations could be derived from admissions data, and that heroin and crack cocaine patients exhibit a decreased likelihood of achieving and maintaining clinical benefit from treatment (Eastwood et al., 2017). One in seven patients (14.5%) were identified as being continuously enrolled in treatment for five years and form the basis of the current study. Taking a longitudinal perspective, the aim of the study is to explore whether or not differential response trajectories can be identified from repeated measures of heroin use frequency across five years of continuous enrolment in treatment in England and, should differing trajectories be identified, whether or not trajectory membership can be predicted from admission covariates and whether or not trajectories are predictive of subsequent recovery from OUD. To achieve these aims, a combination of multilevel Latent Class Growth Analysis (Section 2.6.2), multinomial logistic regression (Section 2.6.3) and multilevel logistic regressions (Section 2.6.4) are utilised.

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4.2 ABSTRACT

Background: This is the first national study in England of continuous long-term opioid substitution treatment (OST).

Methods: All adults admitted to community OST for opioid use disorder (OUD) in 2008/09, with continuous enrolment to 2013/14 (n=7,719). Heroin use trajectories were identified by multilevel Latent Class Growth Analysis. In Year 6 and 7 of follow-up, the outcome measure (analysed by multilevel, multivariable logistic regression) was 'successful completion and no re-presentation' (SCNR) to community treatment within six months.

Results: Five heroin use trajectory classes were identified: '*gradual decreasing*' (20.9%); '*decreasing then increasing*' (21.7%); '*continued low-level*' (17.0%); '*rapid decreasing*' (25.6%), and '*continued high-level*' (14.8%). At the end of Year 7, 4,616 people (60.3%) remained in OST. Of those discharged, 28.8% achieved the SCNR follow-up outcome. SCNR was more likely in the '*gradual decreasing*' (adjusted odds ratio [AOR] 2.40; 95% confidence interval [CI] 1.77-3.26), '*continued low-level*' (AOR 2.46; CI 1.78-3.40) and '*rapid decreasing*' (AOR 3.40; CI 2.43-4.37) classes, relative to the '*continued high-level*' class. SCNR was more likely among patients employed at admission (AOR 1.45; 95% CI 1.15 to 1.83) and those receiving adjunctive psychosocial interventions (AOR 1.44; 95% CI 1.03 to 2.02).

Conclusions: Among English patients in OST for 5-years, heroin use trajectories were clearly delineated, with a gradient of response on the study outcome. Successful completion and no re-presentation was achieved by 28.8% of discharged patients. The rapid decreasing trajectory had the greatest likelihood of positive outcome. Adjunctive psychosocial intervention during OST was associated with positive outcome.

4.3 INTRODUCTION

Oral methadone or buprenorphine are the first-line medical therapies for opioid use disorder (OUD). These opioid substitution treatments (OST) are consistently associated with abstinence from illicit opioid use (e.g. Hubbard et al., 2003; Gossop et al., 2003; Teesson et al., 2006), a lower risk of opioid overdose (White et al., 2015), and reductions in criminal behaviour (Gossop et al., 2005b). Aggregate statistical results may, however, mask differential clinical response among sub-populations. For example, in an English national study of ongoing OUD treatment, 37% of patients were abstaining from heroin during the 28-days before six-month follow-up; a further 31% were using heroin less often; but 29% continued to use heroin at the same frequency as at admission, and 3% had deteriorated (Marsden et al., 2009).

Longer follow-up studies have identified distinct sub-populations of people who share a similar heroin use trajectory. In a US cohort study of 471 heroin users followed-up over 16 years, Hser and colleagues identified three classes: nine per cent were 'early-quitters'; 32% achieved improvements at a later stage in follow-up ('late-decelerated users'), and 59% were labelled 'stably high-level' heroin users with no identifiable improvement (Hser et al., 2007). In a recent 4.5 year follow-up of study of 795 participants in a treatment trial, Hser's group identified the following classes: 'low use' (42.0%); 'high use' (22.3%); 'decreasing use' (18.6%); and 'increasing use' (17.1%), with people in the 'decreasing use' class spending more time in treatment than those in the 'high use' class (Hser et al., 2017). Comparable findings have been reported in Australia (Teesson et al., 2017a).

Recently, we estimated the likelihood of successfully completing OUD within five years among a national cohort of patients (all adults admitted to public treatment services in 2008/09; N=54,357; Eastwood et al., 2017). Approximately 1:7 patients were enrolled

in OST continuously up to the five-year follow-up. In the present study, we report on the status of this cohort and determine follow-up outcomes over the next two years. This is the first national outcome study of long-term, continuous OST in England. To our knowledge, there has been no national study of OST over this time-frame reported elsewhere.

In this report, we aim to:

- (1) identify heroin use response trajectories during five years of OST and estimate associations with patient-level characteristics and treatment exposure;
- (2) estimate whether heroin use response trajectories predict positive outcome during the sixth and seventh year of follow-up.

We hypothesised that: (a) patients with trajectories demonstrating positive response to ongoing OST would be more likely to exit treatment successfully; and (b) adjunctive psychosocial, in-patient and residential interventions would increase the likelihood of completing OST successfully.

4.4 METHODS

4.4.1 DESIGN

This was a seven-year, prospective observational cohort study of all publicly-funded specialist community-setting treatment services providing OST in England reporting to the National Drug Treatment Monitoring System (NDTMS). The study is reported following the RECORD guidelines for observational research using routinely collected health data (Benchimol et al., 2015).

The study cohort is all adults (≥ 18 years; $n=7,877$) diagnosed with OUD (almost all relating to use of heroin) who initiated treatment between 1 April 2008 and 31 March 2009, were continuously enrolled in OST for the next five years (ending 31 March

2014) and then followed-up to 30 September 2016. Following the NDTMS reporting protocol, ‘continuous enrolment’ was defined as either a single unbroken episode of OST, or two or more linked (continuing care) episodes in which there was no more than 21 days between the end of one methadone or buprenorphine prescribing intervention and the start of another (Public Health England, 2015a).

4.4.2 MEASURES

4.4.2.1 DEVELOPMENTAL TRAJECTORY INDICATOR

The Treatment Outcomes Profile (TOP; Marsden et al., 2008) is the English national standard measure for substance use disorder treatment outcomes monitoring. The TOP is a structured clinical interview which is completed at admission, every six months thereafter, and at the completion of treatment. In this study, we used the number of days of heroin use in the 28 days prior to each TOP interview conducted between Year 1 (2008/09) and Year 5 (2013/14).

4.4.2.2 OUTCOME MEASURE

‘Successful completion’ of treatment has been widely used as an outcome measure in effectiveness studies. Definitions vary, but this typically denotes satisfactory resolution of primary clinical problems and agreement between the clinician and patient to exit treatment (e.g. Luchansky et al., 2000; Alterman et al., 2001; Stahler et al., 2016).

The outcome measure in the present study combined two components: successful completion and no re-presentation (SCNR). SCNR is the English national proxy remission measure for OUD treatment outcome monitoring (Public Health England, 2015a). The ‘successful completion’ component was measured in Year 6 and Year 7 (ending 31 March 2016). It was defined as a clinician-verified report of a patient who had completed OST, was in remission from OUD, was abstinent from heroin (and any other non-medical opioids) and cocaine, and had attained their care plan goals. The

‘no re-presentation’ element captures the extent to which the successful completion is sustained by linking patients with a successful completion to the community-based and prison-based treatment databases, as well as the Office for National Statistics’ fatal drug-poisoning database over the subsequent six-month period (ending 30 September 2016), and removing all cases of re-presentation to treatment or fatal overdose from the summative effectiveness measure.

4.4.2.3 BASELINE COVARIATE MEASURES

The following patient demographic, clinical and previous treatment exposure variables (all recorded at initial assessment) were included as potential confounders in the analysis:

Demographic. Sex; age (centred at 18 years and utilised in five-year increments); Black and Minority Ethnicities (BME: a legal monitoring requirement; (*Race Relations (Amendment) Act*, 2000)); employed; housing problems (defined primarily as having no fixed abode, but can also include squatting, short-term hostel/B&B, staying with friends/relatives [homeless, herein]);

Social deprivation. Local area deprivation was measured by the English Indices of Multiple Deprivation (IMD; Department for Communities and Local Government, 2007). IMD data were linked to NDTMS based on the patient’s residential postcode district or the location of their first treatment provider in instances of missing postcode information (see section 3.4.5).

Treatment admission drug use latent class. Four heroin-based latent classes from admission data: (1) heroin low level with concurrent drug disorder; (2) heroin, crack

and alcohol; (3) heroin and crack, and (4) heroin, crack and cannabis. These classes were identified in Eastwood et al. (2017).

Injecting status. Recorded at the start of treatment, as: (1) never injected; (2) lifetime history of injecting; and (3) current injector.

Duration of heroin use 'career'. This was defined as the number of years between first initiation to heroin use and initiating OUD treatment. In the models, this variable was mean centred and utilised in five-year increments.

Treatment history. The patient's referral route into treatment was categorised as: (1) self-referred; (2) criminal-justice system; or (3) other. Whether a patient had previously accessed OUD treatment was also included.

Adjunctive treatment exposure. Together with OST, NDTMS records the following interventions: psychosocial interventions; in-patient detoxification, and residential rehabilitation.

4.4.3 STATISTICAL ANALYSIS

Data management was done with SPSS (version 21). We used multilevel Latent Class Growth Analysis (LCGA) to identify discrete, non-overlapping heroin use change trajectories across five-years of OST (MPlus; version 7). Management of missing data by multiple imputation and all regression analyses was done with Stata (version 13).

4.4.3.1 HEROIN USE TRAJECTORIES

In a longitudinal latent analysis of behaviour change, trajectory membership can be influenced by inclusion of covariates and distal outcomes (Huang et al., 2010).

Following recommendation by Nagin (2005), 1-class through 6-class models were fit to

the data. Each model assumed a Poisson distribution and 5,000 random sets of starting values were used to guard against convergence on local maxima (McLachlan and Peel, 2000). A minimum class size of 5% was set for utility (Borders and Booth, 2012; Willey et al., 2016b).

Trajectory identification was informed by posterior fit statistics. As patients were nested within different local treatment systems, we used multilevel LCGA models and an intra-class correlation coefficient (ICC) was computed for each class (Asparouhov and Muthén, 2007). Multinomial logistic regression then regressed trajectory classes on patient-level characteristics. Robust standard errors were utilised to calculate 95% confidence intervals (CI), to account for clustering of patients in each treatment system (Petersen, 2009).

4.4.3.2 OUTCOME ANALYSIS

A multilevel, multivariable logistic regression model was used to estimate the likelihood of SCNR (Stata command: *meqrlogit*), and the ICC was estimated to assess intercept variation. As a sensitivity analysis, we calculated the E-value from the adjusted odds ratios of the LCGA trajectories and the estimate of its uncertainty from the CIs closest to the null. In this application, the E-value is the minimum strength needed by an unmeasured confounder to account for any significant association between trajectory membership and outcome, conditional on the included covariates (VanderWeele and Ding, 2017).

4.4.3.3 MISSING DATA

LCGA is implemented by full-information maximisation likelihood and can assign patients with at least one measurement to a latent class. However, a complete case analysis may yield biased estimates due to missing covariate data. With no evidence that either the predictors or outcome variables were not missing-at-random (Little and

Rubin, 1987), we created a multiply imputed dataset (Stata command: *MI impute chained*). Logistic regression, multinomial regression, and predictive mean matching were utilised, respectively, for binary, multinomial or continuous covariates with missing data. Twenty probabilistic datasets were imputed, resulting in a relative efficiency of over 98% (Rubin, 1987) and a reduction in power of less than 1% (Graham et al., 2007).

4.5 RESULTS

4.5.1 STUDY COHORT

Patients were recruited from all 149 local treatment systems in England (median 41; interquartile range [IQR] 23-71). The flow of the 7,877 participants continuously enrolled in OST for five years is shown in **Figure 4.1**. Two percent of the cohort (n=158) had no TOP data and were removed. Therefore, LCGA was undertaken on 7,719 cases. A median of 10 TOP interviews were completed (IQR 8-11) and 2,211 patients (28.6%) completed all 11 TOP assessments. A further 58 people (0.7%) were removed as their follow-up status could not be determined.

At the end of Year 7, 4,616 (60.3%) were still enrolled in OST. During Year 6 and 7, 1,987 (25.9%) exited treatment unsuccessfully, and 1,058 (13.8%) successfully completed treatment. Among those successfully completing treatment, 16.5% (n=175) were re-admitted to community treatment in the next six months, five were incarcerated and one person died from opioid-related poisoning. The 'successful completion and no re-presentation' (SCNR) outcome was achieved by 877 (28.8%) of those discharged from OST (n=3,045).

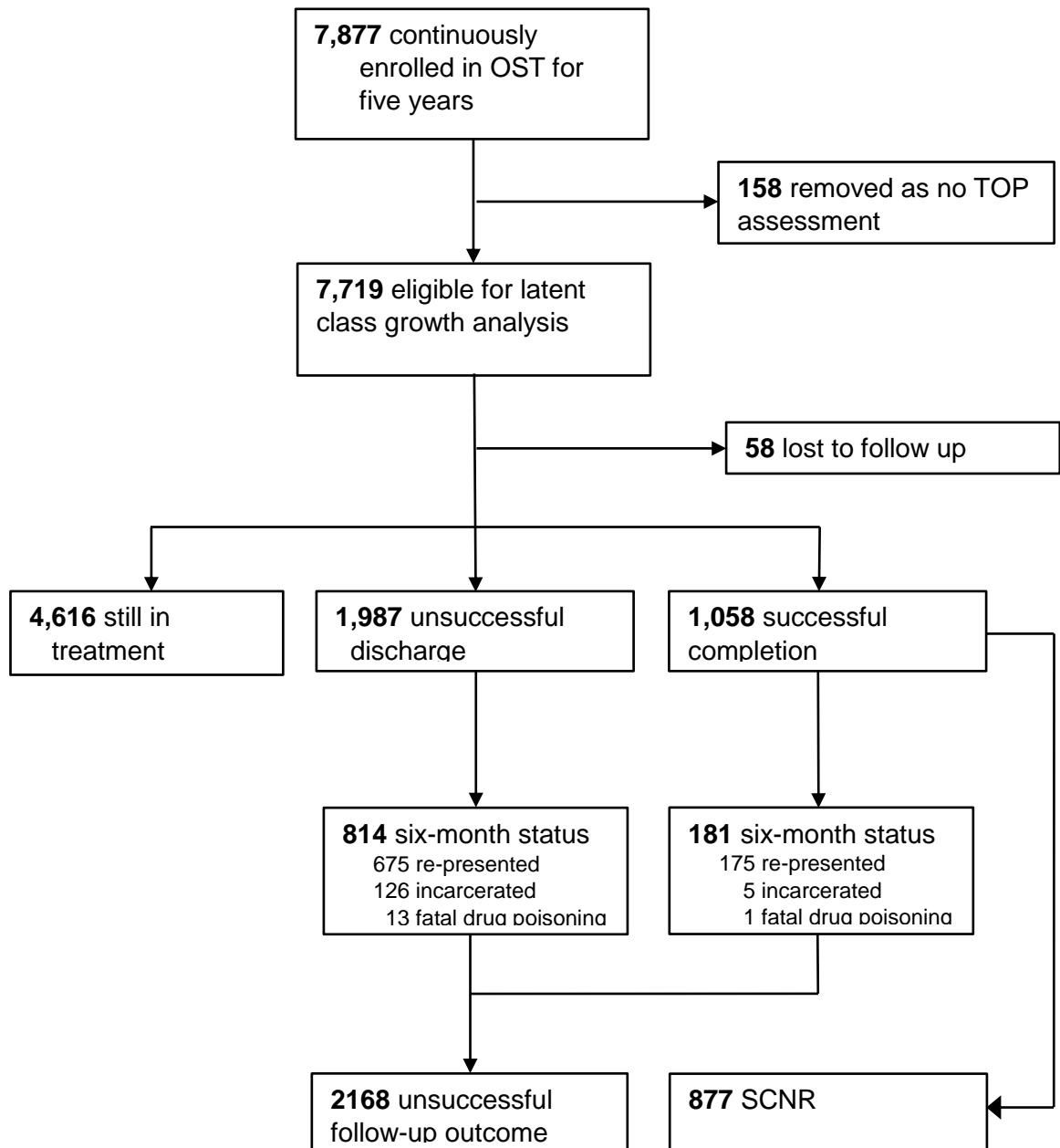


Figure 4.1 Study profile

4.5.2 HEROIN USE DURING FIVE YEARS OF OST

Heroin use was reported by 85.8% of the cohort during the 28-days before the start of treatment (**Table 4.1**). Proportionately, the greatest reduction in heroin was in the first six months of OST, at which point 62.7% were still using. Overall, 39.6% of the cohort were using heroin at Year 3, and there was a slight increase at each six-monthly

assessment to Year 5 (43.2%). The mean number of days used reduced from 19.5 days at intake to 7.4 days at six months and did not exceed four days after 2.5 years in treatment. Correlations over follow-up are shown in **Table 4.2**

4.5.3 HEROIN USE TRAJECTORIES

Table 4.3 displays the results of the multilevel LCGA models. Model indicators pointed to a 6-class solution. However, two classes had consistently low heroin use over the five-years. Accordingly, we judged a parsimonious 5-class model to be optimal. The ICC for classes 1, 2, 4 and 5 ranged between 0.46 and 0.49 and was 0.04 for class 3. We labelled the heroin use trajectory classes as follows (**Figure 4.2**):

- Class 1 (n=1,617, 20.9%: '*gradual decreasing*')
 - Class 2 (n=1,673, 21.7%: '*decreasing then increasing*')
 - Class 3 (n=1,310, 17.0%: '*continued low-level*')
 - Class 4 (n=1,973, 25.6%: '*rapid decreasing*')
 - Class 5 (n=1,146, 14.8%: '*continued high-level*')
 -

Table 4.1 Heroin use during five years of continuous OST (n=7,719)

TOP assessment	Responses (n)	No. (%) using heroin	Mean days used (SD) *
Admission	5,567	4,775 (85.8)	19.5 (11.6)
Year 0.5	5,774	3,622 (62.7)	7.4 (9.7)
Year 1	6,409	3,796 (59.2)	6.0 (8.7)
Year 1.5	6,449	3,673 (57.0)	5.9 (8.6)
Year 2	6,567	3,498 (53.3)	5.4 (8.3)
Year 2.5	6,649	2,899 (43.6)	4.0 (7.5)
Year 3	6,670	2,639 (39.6)	3.5 (6.9)
Year 3.5	6,713	2,729 (40.7)	3.7 (7.1)
Year 4	6,733	2,821 (41.9)	3.6 (7.3)
Year 4.5	6,743	2,873 (42.6)	3.9 (7.2)
Year 5	6,748	2,913 (43.2)	4.0 (7.4)

TOP = Treatment Outcomes Profile; SD = standard deviation

* Mean days of opioid use in past 28 days.

Table 4.2 Correlation matrix of illicit opioid responses across the five-year observation period

	Admission	Year 0.5	Year 1	Year 1.5	Year 2	Year 2.5	Year 3	Year 3.5	Year 4	Year 4.5	Year 5
Admission	1.000										
Year 0.5	0.191	1.000									
Year 1	0.166	0.443	1.000								
Year 1.5	0.123	0.370	0.510	1.000							
Year 2	0.125	0.305	0.382	0.491	1.000						
Year 2.5	0.099	0.261	0.300	0.375	0.478	1.000					
Year 3	0.103	0.235	0.291	0.346	0.372	0.429	1.000				
Year 3.5	0.100	0.214	0.280	0.326	0.369	0.390	0.483	1.000			
Year 4	0.098	0.214	0.262	0.297	0.331	0.333	0.409	0.515	1.000		
Year 4.5	0.104	0.197	0.234	0.263	0.319	0.327	0.347	0.433	0.514	1.000	
Year 5	0.069	0.173	0.215	0.262	0.293	0.283	0.305	0.352	0.422	0.502	1.000

All correlations in the matrix statistically significant at 99% error level (Bonferroni corrected).

Table 4.3 Unconditional multilevel latent class growth analysis of heroin use over five years (n=7,719)

	1-Class	2-Class	3-Class	4-Class	5-Class	6-Class
AIC	886002.87	671087.82	610578.39	580090.68	553248.75	537428.48
BIC	886023.73	671136.50	610654.88	580194.97	553380.86	537588.40
aBIC	886014.20	671114.25	610619.92	580147.31	553320.48	537515.31
Entropy	-	0.975	0.971	0.964	0.950	0.956
Class (probability)						
Class 1	1.00 (1.00)	0.58 (0.99)	0.42 (0.99)	0.24 (0.97)	0.21 (0.97)	0.12 (0.96)
Class 2	-	0.42 (0.99)	0.21 (0.99)	0.37 (0.99)	0.22 (0.97)	0.25 (0.97)
Class 3	-	-	0.37 (0.99)	0.23 (0.97)	0.17 (0.97)	0.18 (0.97)
Class 4	-	-	-	0.16 (0.99)	0.26 (0.94)	0.14 (0.98)
Class 5	-	-	-	-	0.15 (0.98)	0.17 (0.96)
Class 6	-	-	-	-	-	0.15 (0.95)
VLMR	-	<0.01	0.12	<0.01	<0.01	<0.01
BLRT	-	<0.01	<0.01	<0.01	<0.01	<0.01

AIC: Akaike Information Criterion;
 BIC: Bayesian Information Criterion;
 aBIC: sample-size adjusted BIC;
 VLMR: Vuong-Lo-Mendel-Ruben test;
 BLRT: bootstrapped likelihood ratio test.

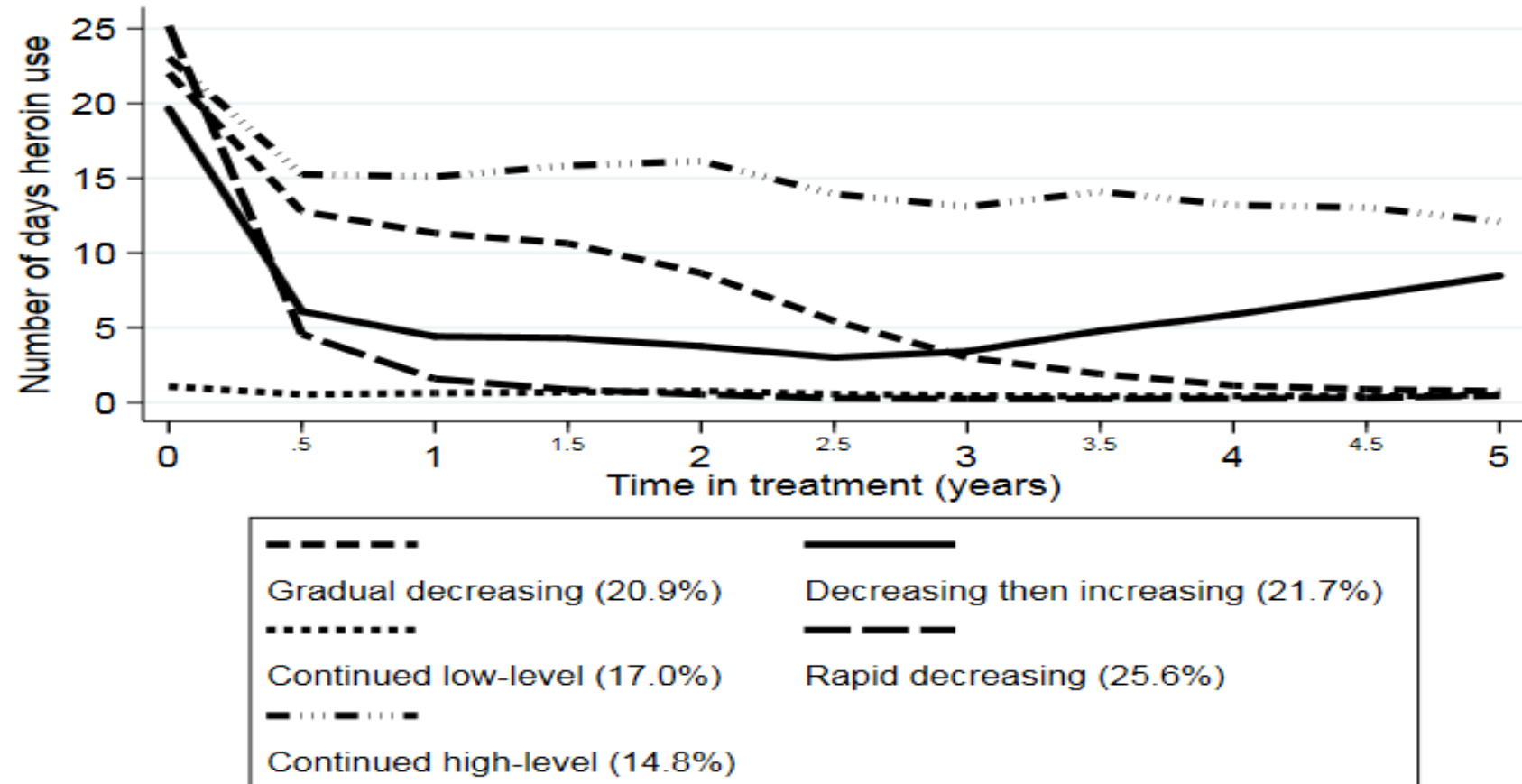


Figure 4.2 Heroin use trajectories over 5 years of continuous OST

Table 4.4 Patient-level characteristics by heroin use trajectories (n=7,719)

Covariate	Total	Continued high-level (n=1,146)	Decreasing then increasing (n=1,673)	Continued low-level (n=1,310)	Gradual decreasing (n=1,617)	Rapid decreasing (n=1,973)
Male	5,562 (72.1)	(72.2)	(75.2)	(72.7)	(70.5)	(70.1)
Age ^a	34.4 (7.9)	34.2 (7.4)	33.9 (7.5)	35.2 (8.3)	33.7 (7.8)	34.9 (8.2)
Black/Minority Ethnic	718 (9.3)	(8.4)	(9.7)	(8.5)	(8.7)	(10.5)
Employed ^b	1,164 (15.7)	(13.7)	(16.9)	(13.3)	(14.1)	(18.5)
Homeless ^c	1,775 (23.4)	(25.4)	(23.7)	(20.6)	(26.1)	(21.5)
Social deprivation:						
Quintile 1 (lowest)	1,935 (25.1)	(23.6)	(25.5)	(25.9)	(25.2)	(24.9)
Quintile 2	1,562 (20.2)	(19.0)	(20.1)	(18.9)	(18.6)	(23.3)
Quintile 3	1,434 (18.6)	(18.1)	(19.4)	(18.2)	(19.2)	(17.9)
Quintile 4	1,595 (20.7)	(20.9)	(21.2)	(20.0)	(21.3)	(20.1)
Quintile 5 (highest)	1,193 (15.5)	(18.5)	(13.8)	(17.0)	(15.7)	(13.8)
Heroin career ^{a,d}	12.3 (7.7)	12.3 (7.2)	11.9 (7.2)	13.3 (8.0)	11.9 (7.4)	12.5 (8.2)
Drug injecting: ^e						
Never	2,290 (29.9)	(25.4)	(31.5)	(27.7)	(27.9)	(34.3)
Lifetime	2,976 (38.9)	(33.3)	(36.6)	(54.5)	(35.7)	(36.5)
Current	2,387 (31.2)	(41.3)	(31.9)	(17.8)	(36.4)	(29.2)
Referral source:						
Other	2,964 (38.4)	(32.6)	(37.2)	(49.5)	(36.2)	(37.2)
Self	3,244 (42.0)	(46.3)	(44.3)	(26.8)	(43.5)	(46.6)
Criminal justice	1,511 (19.6)	(21.2)	(18.5)	(23.7)	(20.3)	(16.2)
Previous OUD treatment	4,871 (63.1)	(72.8)	(64.4)	(59.4)	(65.9)	(56.6)
Drug use sub-population:						
Heroin low-level concurrent drug use disorder	4,295 (55.6)	(55.2)	(56.6)	(53.4)	(54.9)	(57.1)
Heroin, crack and alcohol	388 (5.0)	(4.9)	(5.1)	(4.6)	(6.3)	(4.3)
Heroin and crack	2,589 (33.5)	(34.8)	(32.6)	(36.0)	(32.8)	(32.5)
Heroin, crack and cannabis	447 (5.8)	(5.1)	(5.7)	(6.0)	(5.9)	(6.1)
Adjunctive treatment exposure:						
Psychosocial	7,121 (92.3)	(95.0)	(93.0)	(90.5)	(93.9)	(89.8)
In-patient	566 (7.3)	(11.4)	(7.2)	(5.3)	(8.8)	(5.2)
Residential	109 (1.4)	(3.0)	(1.9)	(0.9)	(1.2)	(0.6)

Figures in parentheses in table are number of participants (percentages) unless otherwise stated. Emboldened percentages and means are statistically significant ($P < 0.05$) from all-case, multiply imputed, multivariable multinomial logistic regression (continued high-level use group as referent). a Year (SD); b Percentage after excluding 286 participants with missing data on this covariate; c Percentage after excluding 123 participants missing data on this covariate; d Percentage after excluding 261 participants missing data on this covariate; e Percentage after excluding 66 participants missing data

4.5.4 PATIENT-LEVEL CHARACTERISTICS

Patient-level characteristics are shown in **Table 4.4**, together with the results of the all-case multinomial logistic regression of the heroin use trajectory classes on patient-level characteristics. Compared to the poor response ('continued high-level') class, participants in the other classes had less previous OUD treatment exposure, and the 'decreasing then increasing', 'continued low-level' and 'rapid decreasing' classes were less likely to be currently injecting at admission.

The 'decreasing then increasing' heroin use class had more men and were less likely to be resident in an area of high social deprivation. The 'continued high-level' heroin use class were more likely to be exposed to psychosocial, in-patient and residential treatments during their enrolment in OST.

4.5.5 TREATMENT STATUS AT THE END OF YEAR 7

Continued enrolment in OST at the end of Year 7 was not associated with heroin use trajectory (**Table 4.5**). Among the treatment leavers, the 'continued high-level' heroin users were most likely to have an unsuccessful discharge. There was an outcome response gradient by class among those who left treatment successfully: successful completion of treatment was recorded for 8.6% of the 'continued high-level' class compared to 18.7% of the 'rapid-decreasing' class. Patients who continuously enrolled at Year 7 were removed from further analysis at this point.

Table 4.5 OST status at Year 7, by heroin use trajectory (n = 7,661)

Heroin use trajectory class	Still enrolled	Unsuccessful discharge	Successful completion
Continued high-level (n=1,142)	678 (59.4)	366 (32.1)	98 (8.6)
Decreasing then increasing (n=1,660)	1,016 (61.2)	482 (29.0)	162 (9.8)
Continued low-level (n=1,298)	803 (61.9)	304 (23.4)	191 (14.7)
Gradual decreasing (n=1,604)	975 (60.8)	388 (24.2)	241 (15.0)
Rapid decreasing (n=1,957)	1,144 (58.5)	447 (22.8)	366 (18.7)
Total	4,616 (60.3)	1,987 (25.9)	1,058 (13.8)

Numbers in parentheses are percentages unless otherwise shown

Compared to the 'rapid decreasing' heroin use class (re-admission rate 11.2%), re-presentation within six months for community treatment was more likely among the 'continued high-level' heroin use class (22.4%; odds ratio [OR] 2.29; 95% CI 1.29-4.08); followed by the 'decreasing then increasing' class (22.2%; OR 2.26; 95% CI 1.38-3.71), the 'gradual decreasing' class (17.3%; OR 1.72; 95% CI 1.08-2.73) and the 'continued low-level' class (17.8%; OR 1.66; 95% CI 1.01-2.72).

4.5.6 IMPACT OF TRAJECTORY MEMBERSHIP ON OUTCOME

The poor responding 'continued high-level' heroin using class had the lowest proportion achieving SCNR (16.2%), followed by the 'decreasing then increasing' group (19.6%). The 'continued low-level use' and 'gradual decreasing use' groups has similar levels of SCNR (31.2% and 31.7%, respectively), while SCNR was most likely to be attained by the 'rapid decreasing' class (39.7%).

The multiply imputed, multilevel logistic regression analysis (**Table 4.6**) indicated that three trajectory groups (i.e. '*gradual decreasing*', '*continued low-level*' and '*rapid decreasing*') were more likely to achieve SCNR compared to the 'continued high-level' class (adjusted odds ratio [AOR] 2.40 [95% CI 1.77 to 3.26]); AOR 2.46 [95% CI 1.78 to 3.40]; AOR 3.26 [95% CI 2.43 to 4.37]), respectively.

The E-value estimate for the 'gradual decreasing use' class was 4.23 (with an uncertainty estimate of 2.94 for the minimum risk ratio needed to shift the CI to the null), E=4.36 (uncertainty estimate = 2.96) for the 'continued low-level use' class and E=5.97 (uncertainty estimate = 4.29) for the 'rapid decreasing use' class. There was also an increased likelihood of achieving SCNR among those with pre-admission employment (AOR 1.45; 95% CI 1.15 to 1.83), those who received adjunctive psychosocial treatment during OST (AOR 1.44; 95% CI 1.03 to 2.02) and a positive association for increasing age (AOR 1.07; 95% CI 1.00 to 2.14). Longer heroin using

career, lifetime history of injecting, and referral from the criminal justice system was associated with a decreased likelihood of achieving SCNR.

4.5.7 POST-HOC ANALYSIS

Finally, we created a binary 'non-response' measure by combining the 'continued high-level use' and 'decreasing then increasing use' trajectory groups against the remaining three trajectory groups. This measure was then collapsed at the local treatment system level, resulting in a range of non-response from 0-70%. Also available at local area level were the prevalence of opiate users per 1,000 population in 2008/09 (Hay et al., 2010), the rate of offending per 1,000 population (Office for National Statistics, 2016), and the rate of drug-related deaths per million population (Public Health England, 2016b). Non-response was regressed on these three measures in a linear regression. The offending rate and the drug-related death rate was not associated with non-response. However, for every extra opiate user per 1,000 population, there was an increase in non-response by almost two percentage points (1.97; 95% CI 0.76 to 3.17).

Table 4.6 Unadjusted and multi-level, all-case multivariable logistic regression

Covariate	Unadjusted OR (95% CI)	All-case AOR (95% CI)
Male	0.90 (0.75, 1.07)	0.95 (0.79, 1.15)
Age	1.03 (0.98, 1.08)	1.07 (1.00, 1.14)
Black/Minority Ethnic	1.03 (0.78, 1.36)	0.94 (0.70, 1.26)
Employed	1.61 (1.29, 1.99)	1.45 (1.15, 1.83)
Homeless	0.79 (0.66, 0.96)	0.88 (0.72, 1.08)
Social deprivation		
Quintile 1 (lowest)	1.06 (0.84, 1.35)	1.07 (0.83, 1.37)
Quintile 2	0.78 (0.60, 1.00)	0.84 (0.64, 1.09)
Quintile 3	0.86 (0.67, 1.10)	0.94 (0.73, 1.22)
Quintile 4	0.82 (0.62, 1.09)	0.89 (0.67, 1.20)
Quintile 5 (highest)	-	-
Heroin career	0.95 (0.90, 1.01)	0.93 (0.87, 1.00)
Drug injecting:		
Never	-	-
Lifetime	0.71 (0.58, 0.86)	0.79 (0.64, 0.97)
Current	0.65 (0.53, 0.80)	0.80 (0.64, 1.00)
Referral source:		
Other	-	-
Self	0.92 (0.77, 1.10)	0.94 (0.78, 1.14)
Criminal justice	0.62 (0.50, 0.79)	0.68 (0.54, 0.87)
Previous OUD treatment	0.73 (0.62, 0.86)	0.87 (0.73, 1.03)
Drug use classification:		
Heroin low level concurrent drug disorder	-	-
Heroin, crack and alcohol	1.05 (0.72, 1.54)	1.02 (0.69, 1.51)
Heroin and crack	1.01 (0.85, 1.20)	0.99 (0.83, 1.19)
Heroin, crack and cannabis	0.93 (0.65, 1.33)	0.87 (0.60, 1.25)
Treatment exposure:		
Psychosocial	1.26 (0.91, 1.75)	1.44 (1.03, 2.02)
In-patient	0.70 (0.52, 0.95)	0.79 (0.57, 1.11)
Residential	0.84 (0.43, 1.64)	1.34 (0.65, 2.76)
Heroin use trajectory class:		
Gradual decreasing	2.37 (1.75, 3.21)	2.40 (1.77, 3.26)
Decreasing then increasing	1.28 (0.93, 1.76)	1.23 (0.89, 1.70)
Continued low-level	2.48 (1.81, 3.40)	2.46 (1.78, 3.40)
Rapid decreasing	3.47 (2.60, 4.64)	3.26 (2.43, 4.37)
Continued high-level	-	-
Model statistics		
Constant	-	0.16 (0.09, 0.29)
Wald χ^2 (d.f. = 25)	-	159.6 - 163.8
LR test χ^2 (d.f. = 1)	-	12.0 - 12.7
Intra-class correlation	-	0.03 - 0.03

4.6 DISCUSSION

In a time of increased focus on recovery (HM Government, 2017; Laudet and Humphreys, 2013), a greater understanding of the heterogeneous response to treatment is required by policy makers, treatment purchasers and clinicians to inform their decision making processes. This report extends our previous study (Eastwood et al., 2017) by estimating heroin use change trajectories over long-term enrolment in OST. We identified five heroin use trajectory groups and found that the trajectory groups tending towards abstinence at Year 5 were significantly more likely to achieve a sustained benefit from treatment (SCNR follow-up outcome).

4.6.1 INTEGRATION WITH THE LITERATURE

In the treatment literature, several demographic and patient-level characteristics have been linked to developmental trajectories associated with relatively poor treatment response, including: males; people from some ethnic minorities; lower educational achievement; earlier onset of drug use, and involvement with the criminal justice system (Grella and Lovinger, 2011; Hser et al., 2008b, 2007).

Our ‘continued low-level’, ‘continued high-level’ and ‘decreasing then increasing’ classes are similar to the ‘low use’, ‘high use’ and ‘increasing use’ response groups identified by Hser’s group (Hser et al., 2008b). Other studies have also highlighted a sub-population that does not exhibit substantial reduction in drug use, as well as a group demonstrating rapid reductions (Grella and Lovinger, 2011; Teesson et al., 2017a). This points to a degree of phenotypic similarity across different countries, settings and cohort characteristics. Similar to the Australian study (Teesson et al., 2017a), we note that few baseline covariates predict trajectory membership, although higher deprivation, currently injecting, and previous treatment were associated with relative non-response to treatment.

The validity of person-centred latent trajectory modelling has been criticised (Sher et al., 2011). Our finding that more favourable trajectory memberships are associated with sustained benefit provides support for the predictive validity of the approach. It also extends previous work documenting associations with decreased mortality and better employment, substance use and mental health outcomes (Hser et al., 2007; Teesson et al., 2017a; Hser et al., 2017), and highlights the importance of incorporating independent outcomes in person-centred research design.

Our findings also highlight the positive role of employment in recovery, although it is interesting that stable housing did not affect the likelihood of recovery as in other studies (e.g. Cloud and Granfield, 2008). Injecting and criminal justice referrals were, as expected (Marsden et al., 2012a), negatively associated with positive outcome.

4.6.2 CLINICAL IMPLICATIONS

In our study, we estimate that one in seven patients demonstrate sustained non-response over significant periods of time and a further fifth of patients exhibit a tendency to deteriorate after three years of treatment. Continued illicit opioid use on top of an opioid prescription is a recognised problem (Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group, 2017). It is important for clinicians to identify non-response at an early stage and to review and optimise the treatment care package. Several clinical responses are available, including: increasing the dose; dividing the dose into smaller daily doses in the case of faster metabolism; offering to change the OST medication, and reintroducing daily supervised consumption (ibid). Service user views on medication should be taken into account, as a quarter consider the OST dose to be 'poor or bad' (Advisory Council on the Misuse of Drugs, 2015). In the US, around a quarter of patients also receive methadone doses too low to be effective (D'Aunno et al., 2014).

4.6.3 POLICY IMPLICATIONS

Our finding that more than 40% of patients continue to use illicit opioids after five years of continuous treatment supports the conclusion that a blanket time limit on prescribing would not be clinically appropriate (Advisory Council on the Misuse of Drugs, 2014). National drug treatment administrators should make available performance monitoring reports for clinics and treatment purchasers focused on long-term use of illicit opioids, which could aid local planning, resource allocation and improve outcomes. Further, incorporation of prescription dose into the NDTMS would help estimate whether, and to what degree, sub-optimal dosing is associated with continued use on top.

Our finding that psychosocial interventions, received by most but not all patients, is advantageous for sustaining recovery underscores the importance of comprehensive interventions being made available in the treatment of OUD. More frequent or personalised psychosocial interventions may also be of benefit (Marsden et al., 2017). Treatment clinics may benefit from an audit of clinical practices as it has been suggested that interventions are 'front-loaded' and less intensive support is available to those in treatment over longer periods (Finch, 2003).

In the current study, it appears that areas with a greater degree of non-response are also affected by a larger opiate-using population. Although we are unable to determine a precise mechanism, there may be social network influences in operation to explain this association. For example, heroin users who have achieved abstinence often cite moving away from drug-using social networks as a factor in their success (Best et al., 2008). Greater integration of treatment services with local recovery groups may help mitigate this influence.

4.6.4 STRENGTHS AND LIMITATIONS

A major study strength is the national, large-scale, long-term follow-up of all individuals accessing treatment for opioid use disorder in England. In addition, the consent model supporting NDTMS enables cross-referencing with subsequent treatment admissions and drug-poisoning databases, providing the utility to examine an objective summative measure of sustained recovery from OUD.

Several limitations are also acknowledged: first, while all available covariates in NDTMS were screened in the present analysis, other covariates could further elucidate the likelihood of sustaining recovery, including treatment motivation (Simpson and Joe, 1993), engagement (Simpson et al., 1995) and other recovery strengths (Gossop et al., 2002). Second, it is possible that other interventions, such as attending Narcotics Anonymous, were experienced by the patients in this cohort. These interventions are not, however, captured by NDTMS and it is not possible to assess the potential impact these may have had. We note that the E-value parameter suggests such a variable would need to have an adjusted odds ratio of at least 2.9 to mitigate the association between trajectory membership and outcome.

4.6.5 CONCLUSIONS

This study highlights the importance of research analytical methods that capture longitudinal trajectories. Within a cohort of patients continuously enrolled in treatment for five years, diverse treatment-response trajectories emerge. The differential association between trajectory membership and subsequent outcomes has real application and could be important to clinicians and treatment purchasers as it indicates a substantial proportion of patients exhibit chronic or relapsing opioid use in response to treatment and may require more intensive interventions over a longer period.

Chapter 5 STUDY 3: CHANGE IN ALCOHOL AND OTHER DRUG USE DURING FIVE YEARS OF CONTINUOUS OPIOID SUBSTITUTION TREATMENT

5.1 DESCRIPTION OF STUDY IN THE CONTEXT OF THE THESIS

The previous chapter focused on the response trajectories of heroin use frequency over the course of five years of continuous enrolment in treatment. Heroin users are, however, a heterogeneous group in terms of adjunctive substance use. Indeed, as noted in Chapter 3, some 67% of heroin users had a concurrent substance use disorder at the point of treatment admission. As it may prove informative to clinical and policy decision making, the current study examines whether or not Latent Class Growth Analysis can also identify differing trajectory groups based on their use of the other substances recorded via the Treatment Outcomes Profile i.e. crack cocaine, cocaine powder, amphetamines, cannabis, alcohol, as well as a further unspecified substance.

This chapter was published as follows:

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5.2 ABSTRACT

Background: English national prospective, observational cohort study of patients continuously enrolled for five years in opioid substitution treatment (OST) with oral methadone and sublingual buprenorphine. This is a secondary outcome analysis of change in use of alcohol and other drug use (AOD) following identification of heroin use trajectories during OST.

Methods: All adults admitted to community OST in 2008/09 and enrolled to 2013/14 (n=7,717). Data from 11 sequential, six-monthly clinical reviews were used to identify heroin and AOD use trajectories by multi-level Latent Class Growth Analysis. OST outcome in the sixth and seventh year was 'successful completion and no re-presentation' (SCNR) to structured treatment and was assessed using multi-level logistic regression.

Results: With 'rapid decreasing' heroin use trajectory as referent, 'continued high-level' heroin use predicted 'continued high-level' crack cocaine use (relative risk ratio [RRR] 58.7; 95% confidence interval [CI] 34.2-100.5), 'continued high-level' alcohol use (RRR 1.2; 95% CI 1.0-1.5), 'increasing' unspecified drug use (RRR 1.7; 95% CI 1.4-2.1) and less 'high and increasing' cannabis use (RRR 0.5; 95% CI 0.4-0.6). 'Increasing' crack use was negatively associated with SCNR outcome for the 'decreasing then increasing' and 'gradual decreasing' heroin use groups (adjusted odds ratio [AOR] 0.5; 95% CI 0.3-0.9 and AOR 0.2; 95% CI 0.1-0.7, respectively).

Conclusions: Continued high-level heroin use non-response during long-term OST is associated with high-level crack cocaine and alcohol use, increasing unspecified drug use, but less high and increasing cannabis use. Increasing use of crack cocaine is negatively associated with the likelihood that long-term OST is completed successfully.

5.3 INTRODUCTION

Opioid substitution treatment (OST), with oral methadone or sublingual buprenorphine, is the first-line maintenance intervention for opioid use disorder (OUD). Observational studies have consistently reported OST to be associated with suppression of illicit opioid use (e.g. Hubbard et al., 2003; Mattick et al., 2014, 2009; Simpson et al., 1982; Teesson et al., 2006), a lower risk of opioid overdose (White et al., 2015), and reductions in crime (Russolillo et al., 2018).

Many people with OUD present for treatment with problems associated with several substance classes. Darke and Hall (1995) reported that 99% of heroin users had used another drug class in the six-months before treatment and reported using an average of 5.2 other substances. In England, national statistics demonstrate that crack cocaine is the most prevalent of concurrent substance use disorders and has increased in those starting treatment from 42% to 54% in the four years to 2017/18 (Public Health England [PHE], 2018a, 2017, 2016, 2015). Crack cocaine use during treatment for OUD is associated with poorer suppression of illicit opioid use, worse acquisitive crime and psychological health outcomes and a lowered likelihood of completing treatment successfully (Eastwood et al., 2017; Gossop et al., 2002a; Heidebrecht et al., 2018; Marsden et al., 2012b, 2009). Concurrent alcohol use disorder has been reported to affect around a third of OUD patients in treatment, although in England the prevalence is somewhat lower at 17% (Nolan et al., 2016; Public Health England, 2018a).

There have been mixed findings from observational follow-up studies of change in concurrent alcohol and other drug use (AOD) during OUD treatment. Brecht et al. (2008) observed an aggregate reduction in use, while Gossop et al. (2003) reported a return to baseline levels following a temporary reduction, and others have reported a worsening state in a subset of non-users at treatment admission (Gossop et al., 2002b;

Weiss et al., 2015). A two-year study of heroin users enrolled in the Australian Treatment Outcomes Study reported that reductions in heroin use were not associated with increases in the use of cocaine, amphetamine, cannabis, benzodiazepines and other opioids (Darke et al., 2006). A longer 11-year follow-up study reported the use of alcohol was to be consistent across waves, ranging between 49% and 56% (Darke et al., 2015). Similar reductions in alcohol and other drug use has been reported in Ireland over a 3-year follow-up period (Comiskey et al., 2009).

Aggregated findings may, however, mask differential clinical response among sub-populations. In their classic 30-year study of heroin and other drug use, Grella and Lovinger (2011) reported that a quarter of those followed up tracked a 'rapid decrease' heroin use trajectory and over half of these reported an early increase in AOD (although specific non-opioid substance classes were not reported). Recently, Teesson et al. (2017) identified six heroin use trajectory groups over 11-years. They reported that those following the 'no decrease' track were more likely to have been incarcerated and to be currently affected by unstable housing and to be using benzodiazepines, but did not examine longitudinal patterns of concurrent substance use.

In a recent report in this journal, we identified five heroin use trajectories in a national cohort of patients who were continuously enrolled in OST for five years ($n=7,719$; Eastwood et al., 2018). We showed that patients following a positive treatment response trajectory towards abstinence were more likely to successfully complete treatment in the subsequent two-year period.

To inform clinical practice and treatment policy, studies are needed to determine specific substance use change trajectories during long-term OUD treatment. Accordingly, in this related article, we determined the strength of evidence:

- (1) for a trajectory of patients characterised by increasing use of alcohol, cannabis, crack cocaine, cocaine powder, amphetamines and any unspecified drug use;
- (2) that positive and negative change in heroin use is associated with an increase in alcohol and other drug use; and
- (3) increased use of alcohol and other drug use predicts poor OST outcome.

5.4 METHODS

5.4.1 DESIGN

Using data from the English National Drug Treatment Monitoring System (NDTMS), this was a national, seven-year, prospective cohort study reported following the RECORD guidelines for observational research using routinely collected health data (Benchimol et al., 2015). The study cohort has been described in two previous reports in the journal where a detailed description of measures is presented (Eastwood et al., 2018, 2017).

The present analysis concerns all patients who initiated OST between 1 April 2008 and 31 March 2009 and were enrolled for five years, ending 31 March 2014 and followed-up to 30 September 2016 (7,719 [14.2%] of 54,357). Following the NDTMS reporting protocol, all members of the cohort were either continuously enrolled in OST (i.e. they had a single unbroken episode of OST), or there was no more than 21 days between the end of one prescribing episode and the initiation of another (i.e. in the context of a transfer of a patient from one OST prescribing service to another).

5.4.2 MEASURES

5.4.2.1 DEVELOPMENTAL TRAJECTORY INDICATORS

The Treatment Outcomes Profile (TOP; Marsden et al., 2008) is a structured, clinical interview for substance use disorder treatment monitoring. Using a recall period of the

past 28 days, the TOP is completed by the clinician at the patient's admission; then as part of a clinical review conducted every six months, and at treatment completion.

There were 11 TOP interviews conducted between Year 1 (2008/09) and Year 5 (2013/14) recording the number of days the patient reported using alcohol, cannabis, crack cocaine, cocaine powder, amphetamines, and any unspecified drug. The latter drug category is known only at the level of the treatment clinic. However, annual aggregate data suggest it is likely to involve benzodiazepines rather than anti-depressants, hallucinogens, volatile solvents, or major tranquillisers (10% prevalence versus <1%, respectively; Public Health England, 2018).

For the present analysis, we used the following five heroin use trajectory classes identified by Eastwood et al. (2018; **Figure 5.1**)¹:

- Class 1 (n=1,617, 20.9%: *'gradual decreasing'*)
- Class 2 (n=1,672, 21.7%: *'decreasing then increasing'*)
- Class 3 (n=1,310, 17.0%: *'continued low-level'*)
- Class 4 (n=1,973, 25.6%: *'rapid decreasing'*)
- Class 5 (n=1,145, 14.9%: *'continued high-level'*)

¹ Due to two individuals with no AOD data, the 'decreasing then increasing' and 'continued high-level' classes were each reduced by one individual for the present analysis.

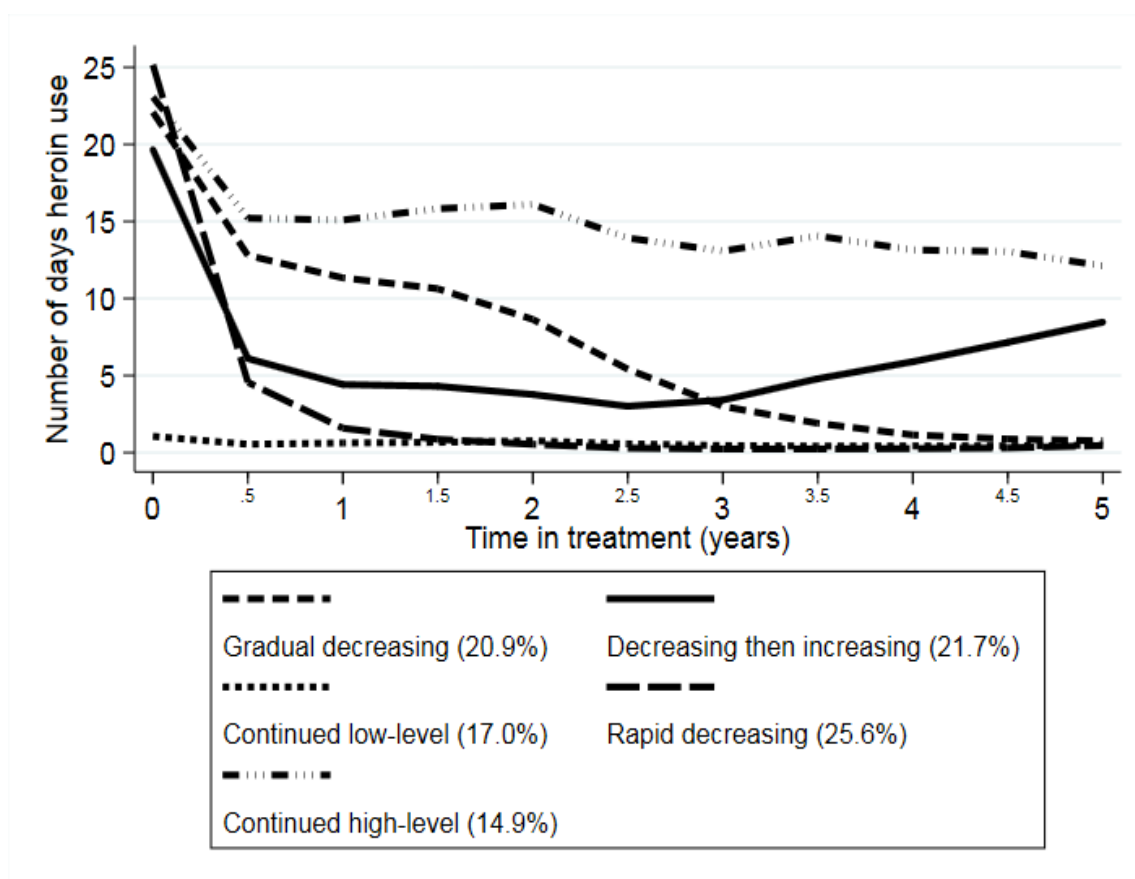


Figure 5.1 Heroin use trajectories over 5 years of continuous OST

5.4.2.2 OUTCOME MEASURE

The OST outcome was the national summative measure of treatment effectiveness defined as successful completion and no re-presentation (SCNR) for further treatment within six months (Public Health England, 2018f). 'Successful completion' was recorded in Year 6 and Year 7 (ending 31 March 2016) by a clinician-verified report indicating: (1) abstinence from heroin (and any other non-medical opioids) and cocaine; (2) remission from OUD; (3) attainment of personal care plan goals and (4) completion of OST. For this summative measure of OST effectiveness, we removed all individuals to 30 September 2016 who were re-admitted to community-based or prison-based treatment, or were recorded on the Office for National Statistics' fatal drug-poisoning database.

5.4.2.3 BASELINE COVARIATE MEASURES

Patient-level variables in the analysis included demographics (sex, age, ethnicity, employment, homelessness); social deprivation (linked to NDTMS based on the patient's residential postcode district or the location of their first treatment provider in instances of missing postcode information; see section 3.4.5); treatment admission latent drug use class from Eastwood et al. (2017); drug injecting status; duration of heroin use 'career'; referral route; other interventions (psychosocial; in-patient detoxification; or residential rehabilitation); and previous treatment for OUD.

5.4.2.4 STATISTICAL ANALYSIS

Data management was done with SPSS (version 21). Given the clustering of patients within local treatment systems, we used multi-level Latent Class Growth Analysis (LCGA) to identify discrete, non-overlapping AOD use change trajectories across the five-years of OST (MPlus; version 7). Management of missing data (by multiple imputation) and all regression analyses was done with Stata (version 15.1).

5.4.2.5 AOD USE TRAJECTORIES

Sequentially, 1-class through 6-class models were fit to the data to identify unconditional trajectory membership. A Poisson distribution was assumed for all models and 5,000 random sets of starting values were used to guard against convergence on local maxima (McLachlan and Peel, 2000). The LCGA approach aims to converge on what is termed the 'global maximum', which is the set of parameter estimates associated with the largest loglikelihood for the entire curve being estimated (Jung and Wickrama, 2008). In effect, the LCGA algorithm can get stuck on an incorrect solution if it erroneously considers the maximum loglikelihood of only part of a curve to be the maximum of the entire curve. The LCGA algorithm cannot distinguish between local and global maxima, which is why a high number of random starts can only protect against, rather than fully eliminate, the risk of an incorrect solution.

Trajectory identification was informed by the Aikaike and Bayesian information criteria (AIC and BIC), entropy and the Vuong-Lo-Mendel-Ruben (VLMR) and bootstrapped likelihood ratio tests (BLRT).

AIC and BIC are relative fit indices and, as such, require more than a single model for their utility to become apparent (Sen and Bradshaw, 2017). Both criteria are useful, particularly when exploring a new dataset as the BIC is expected to perform better when the true model has a simple structure or is present among the set of candidate models which the AIC is expected to perform better when the true model has a complex structure or is absent from the set of candidate models (Sen and Bradshaw, 2017; Vrieze, 2012).

Entropy is a measure of how well the LCGA model assigns individuals to a given trajectory group. It is possible, for example, to assign a given individual an equal probability of being in each of the identified classes. This would have low entropy as the model cannot 'decide' in which class to best place the individual. In contrast, should an individual be assigned a 100% probability of being in one class and 0% for all remaining classes, the entropy score would be high as the model was quite certain. The VLMR and BLRT specifically test whether a model with k classes provides a significantly better fitting solution than a model with $k-1$ classes. A minimum class size of 5% of the cohort was pre-specified for utility (Borders and Booth, 2012; Willey et al., 2016b) as it was decided that any class with less than this proportion, while potentially interesting, does not readily lend itself to policy decision making.

5.4.2.6 MISSING DATA

As LCGA is implemented by full-information maximisation likelihood, all patients with at least one measurement could be assigned to a latent class, but a complete case

sample may yield biased estimates due to missing covariate data. As such, and with no evidence that missing data was not missing-at-random, a set of twenty multiply imputed datasets was created using logistic regression, multinomial regression, and predictive mean matching for missing binary, multinomial or continuous data, respectively (Stata command: *MI impute chained*).

5.4.2.7 ANALYSIS OF HEROIN AND AOD USE TRAJECTORIES

A series of multiply imputed, multivariable, multinomial logistic regressions regressed AOD use trajectory classes on heroin use trajectory groups, controlling for patient-level characteristics (Stata command: *mlogit*). Robust standard errors were utilised to calculate 95% confidence intervals (CI) to adjust for clustering of patients in each treatment system. Multiply imputed, multilevel, multivariable logistic regression models were used to estimate the likelihood of SCNR (Stata command: *meqrlogit*). As the likelihood of SCNR varied by heroin use trajectory, we estimated the association between AOD use trajectory groups and SCNR for each group.

5.5 RESULTS

5.5.1 STUDY COHORT

The study cohort includes 7,719 patients for which heroin use trajectories were identified (sample details in Eastwood et al. 2018). These patients were recruited from all 149 local treatment systems in England (median 41; interquartile range [IQR] 23-71). Two patients did not complete a TOP assessment across all 11 assessment periods and were removed. Multilevel LCGA models were undertaken on 7,717 patients. A further 58 patients (0.8%) were subsequently removed as their original treatment records from 2008/09 were no longer available on NDTMS when assessing their follow-up status.

5.5.2 HEROIN AND AOD USE DURING FIVE YEARS OF CONTINUOUS OST

Heroin use was reported by 85.8% of the cohort during the 28-days preceding treatment admission (**Table 5.1**). The most prevalent substances reported in the pre-admission month were alcohol (41.7%), crack cocaine (40.3%), cannabis (27.2%) and unspecified drugs (19.7%). Less than 5% reported using cocaine powder or an amphetamine.

At the end of Year 5, the prevalence of heroin use fell by almost half to 43.2%. The largest reduction in AOD use was observed for crack cocaine (20.6%), unspecified drugs (12.0%) and cannabis (6.7%). The prevalence of alcohol use was reduced by 2.7%. Although cocaine powder and amphetamines were reduced by 2.1% and 1.5%, respectively, this represented a reduction of over a third (36.6%) for amphetamines and nearly a half (44.7%) for cocaine powder. Due to the marginal prevalence of amphetamines and cocaine powder use in the cohort, these substances were not included in the models.

5.5.3 AOD USE TRAJECTORIES

Table 5.2 displays the results of the multilevel LCGA models for alcohol, crack cocaine, cannabis and unspecified drug. For each substance, AIC, BIC, aBIC, entropy and BLRT indicators all pointed to six-class solutions. However, based on the model indicators, as well as the longitudinal separation between trajectory groups, we judged that alcohol, crack cocaine, cannabis and unspecified drug were best described by a more parsimonious four, five, three and three class model, respectively.

Figure 2 (charts A-D) show the following trajectory classes:

Alcohol (Figure 2A: Class 1 [n=1,323, 17.1%: '*continued high-level*']; Class 2 [n=3,810, 49.4%: '*continued low-level*']; Class 3 [n=1,230, 15.9%: '*increasing*']; Class 4 [n=1,354, 17.6%: '*decreasing*']).

Crack cocaine (Figure 2B: Class 1 [n=735, 9.5%: '*gradual decreasing*']; Class 2 [n=924, 12.0%: '*increasing*']; Class 3 [n=4,576, 59.3%: '*continued low-level*']; Class 4 [n=407, 5.3%: '*continued high-level*']; Class 5 [n=1,075, 13.9%: '*rapid decreasing*']).

Cannabis (Figure 2C: Class 1 [n=4,565, 59.2%: '*continued low-level*'], Class 2 [n=1,834, 23.8%: '*low and decreasing*'], Class 3 [n=1,318, 17.1%: '*high and increasing*']).

Unspecified drug use (Figure 2D: Class 1 [n=1,047, 13.6%: '*increasing*'], Class 2 [n=5,490, 71.1%: '*continued low-level*'], Class 3 [n=1,180, 15.3%: '*decreasing*']).

Table 5.1 Heroin, alcohol and other drug use during five years of continuous OST (n=7,717)

Substance	Treatment Outcomes Profile assessment										
	Admission	Year 0.5	Year 1	Year 1.5	Year 2	Year 2.5	Year 3	Year 3.5	Year 4	Year 4.5	Year 5
Heroin responses (n)	5567	5774	6409	6449	6567	6649	6670	6712	6733	6742	6746
% using	85.8	62.7	59.2	57.0	53.3	43.6	39.6	40.6	41.9	42.6	43.2
Mean days using (SD) *	19.5 (11.6)	7.4 (9.7)	6.0 (8.7)	5.9 (8.6)	5.4 (8.3)	4.0 (7.5)	3.5 (6.9)	3.7 (7.1)	3.6 (7.0)	3.9 (7.2)	4.0 (7.4)
Alcohol responses (n)	5496	5758	6407	6450	6569	6652	6675	6716	6737	6748	6739
% using	41.7	43.3	43.3	42.5	41.9	42.5	42.3	41.2	40.9	40.2	39.0
Mean days using (SD) *	5.4 (9.3)	5.2 (8.9)	5.3 (9.0)	5.2 (9.0)	5.3 (9)	5.3 (9.1)	5.5 (9.3)	5.3 (9.2)	5.4 (9.2)	5.3 (9.3)	5.3 (9.3)
Crack responses (n)	5511	5761	6401	6444	6565	6642	6667	6708	6728	6738	6740
% using	40.3	25.1	20.4	20.3	20.3	19.6	19.2	19.2	19.1	19.2	19.7
Mean days using (SD) *	4.5 (8.5)	2.0 (5.4)	1.5 (4.4)	1.5 (4.5)	1.5 (4.7)	1.4 (4.5)	1.5 (4.6)	1.4 (4.3)	1.4 (4.3)	1.4 (4.4)	1.4 (4.5)
Cannabis responses (n)	5463	5741	6391	6434	6555	6643	6670	6709	6721	6735	6731
% using	27.2	24.3	23.5	22.3	21.2	22.3	22.4	22.1	21.3	21.8	20.5
Mean days using (SD) *	3.8 (8.4)	3.5 (8.3)	3.5 (8.4)	3.4 (8.1)	3.2 (8.0)	3.4 (8.2)	3.5 (8.3)	3.5 (8.4)	3.4 (8.3)	3.5 (8.3)	3.2 (8.0)
Unspecified drug responses (n)	5395	5684	6356	6407	6554	6627	6654	6695	6713	6710	6703
% using	19.7	9.5	8.3	7.3	7.4	6.9	7.1	7.3	7.2	7.9	7.7
Mean days using (SD) *	3.3 (8.1)	1.7 (6.3)	1.3 (5.6)	1.2 (5.4)	1.2 (5.2)	1.1 (5.0)	1.1 (4.9)	1.0 (4.9)	1.1 (5.0)	1.1 (5.0)	1.1 (5.1)
Cocaine powder responses (n)	5438	5736	6391	6435	6559	6635	6655	6686	6700	6705	6701
% using	4.7	3.2	2.5	2.3	2.3	2.7	2.4	2.6	2.4	2.6	2.6
Mean days using (SD) *	0.2 (1.8)	0.1 (0.9)	0.1 (0.8)	0.1 (0.9)	0.1 (0.9)	0.1 (0.9)	0.1 (1.1)	0.1 (0.9)	0.1 (0.8)	0.1 (1.0)	0.1 (0.9)
Amphetamines responses (n)	5434	5734	6390	6434	6559	6637	6660	6692	6700	6708	6705
% using	4.1	2.7	2.5	2.8	2.6	2.5	2.8	2.3	2.3	2.5	2.6
Mean days using (SD) *	0.4 (2.6)	0.1 (1.4)	0.2 (1.5)	0.2 (1.6)	0.2 (1.6)	0.2 (1.7)	0.2 (1.8)	0.2 (1.5)	0.2 (1.7)	0.2 (1.8)	0.2 (1.9)

SD = standard deviation

* Mean days of use in past 28 days

Table 5.2 Unconditional multilevel latent class growth analysis of alcohol and other drug use over five years (n=7,717)

Substance	Post-hoc criteria						Class proportion (probability of assignment)					
	AIC	BIC	aBIC	Entropy	VLMR	BLRT	1	2	3	4	5	6
Alcohol												
Class 1	1035730.70	1035751.55	1035742.02	-	-	-	1.00 (1.00)					
Class 2	596761.37	596810.03	596787.78	0.994	<0.0001	<0.0001	0.67 (1.00)	0.33 (1.00)				
Class 3	518637.67	518714.13	518679.18	0.985	0.293	<0.0001	0.29 (0.99)	0.51 (1.00)	0.20 (0.99)			
Class 4	488513.21	488617.47	488569.81	0.980	0.135	<0.0001	0.17 (0.99)	0.49 (1.00)	0.16 (0.98)	0.18 (0.98)		
Class 5	466197.73	466329.81	466269.43	0.971	0.650	<0.0001	0.11 (0.97)	0.14 (0.99)	0.12 (0.98)	0.24 (0.97)	0.40 (0.99)	
Class 6	450851.39	451011.27	450938.18	0.967	0.200	<0.0001	0.12 (0.99)	0.11 (0.97)	0.15 (0.95)	0.09 (0.97)	0.14 (0.96)	0.40 (0.99)
Crack cocaine												
Class 1	521547.29	521568.15	521558.61	-	-	-	1.00 (1.00)					
Class 2	317093.91	317142.57	317120.33	0.988	<0.0001	<0.0001	0.27 (1.00)	0.73 (1.00)				
Class 3	272328.31	272404.78	272369.82	0.979	0.057	<0.0001	0.10 (0.99)	0.26 (0.98)	0.64 (1.00)			
Class 4	252515.88	252620.15	252572.48	0.974	<0.05	<0.0001	0.15 (0.96)	0.08 (0.99)	0.63 (1.00)	0.14 (0.97)		
Class 5	241212.70	241344.77	241284.40	0.965	0.210	<0.0001	0.10 (0.96)	0.12 (0.96)	0.59 (0.99)	0.05 (0.98)	0.14 (0.94)	
Class 6	233444.82	233604.70	233531.61	0.958	0.536	<0.0001	0.05 (0.98)	0.07 (0.96)	0.14 (0.93)	0.09 (0.90)	0.56 (0.99)	0.09 (0.97)
Cannabis												
Class 1	938291.53	938312.38	938302.85	-	-	-	1.00 (1.00)					
Class 2	535324.30	535372.95	535350.71	0.994	<0.0001	<0.0001	0.28 (1.00)	0.72 (1.00)				
Class 3	464870.58	464947.04	464912.09	0.988	0.319	<0.0001	0.59 (1.00)	0.24 (0.99)	0.17 (0.99)			
Class 4	432664.99	432769.26	432721.59	0.986	<0.05	<0.0001	0.13 (0.98)	0.14 (0.98)	0.60 (1.00)	0.13 (0.99)		
Class 5	412930.72	413062.79	413002.41	0.982	0.305	<0.0001	0.57 (1.00)	0.11 (0.98)	0.09 (0.99)	0.13 (0.97)	0.10 (0.98)	
Class 6	397768.05	397927.93	397854.84	0.983	0.103	<0.0001	0.56 (1.00)	0.07 (0.99)	0.08 (0.98)	0.11 (0.97)	0.11 (0.97)	0.08 (0.98)
Unspecified drug												
Class 1	539800.54	539821.40	539811.86	-	-	-	1.00 (1.00)					
Class 2	348344.25	348392.91	348370.66	0.991	<0.0001	<0.0001	0.27 (0.99)	0.73 (1.00)				
Class 3	297333.74	297410.20	297375.25	0.986	0.217	<0.0001	0.14 (0.99)	0.71 (1.00)	0.15 (0.98)			
Class 4	269356.09	269460.36	269412.70	0.985	0.623	<0.0001	0.69 (1.00)	0.07 (0.99)	0.10 (0.99)	0.14 (0.97)		
Class 5	246710.61	246842.68	246782.31	0.981	0.409	<0.0001	0.68 (1.00)	0.09 (0.98)	0.98 (0.96)	0.99 (0.99)	0.98 (0.98)	
Class 6	230945.90	231105.78	231032.69	0.980	0.0187	<0.0001	0.05 (0.99)	0.68 (1.00)	0.05 (0.99)	0.10 (0.95)	0.05 (0.97)	0.06 (0.97)

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; aBIC: sample-size adjusted BIC; VLMR: Vuong-Lo-Mendel-Ruben test; BLRT: bootstrapped likelihood ratio test.

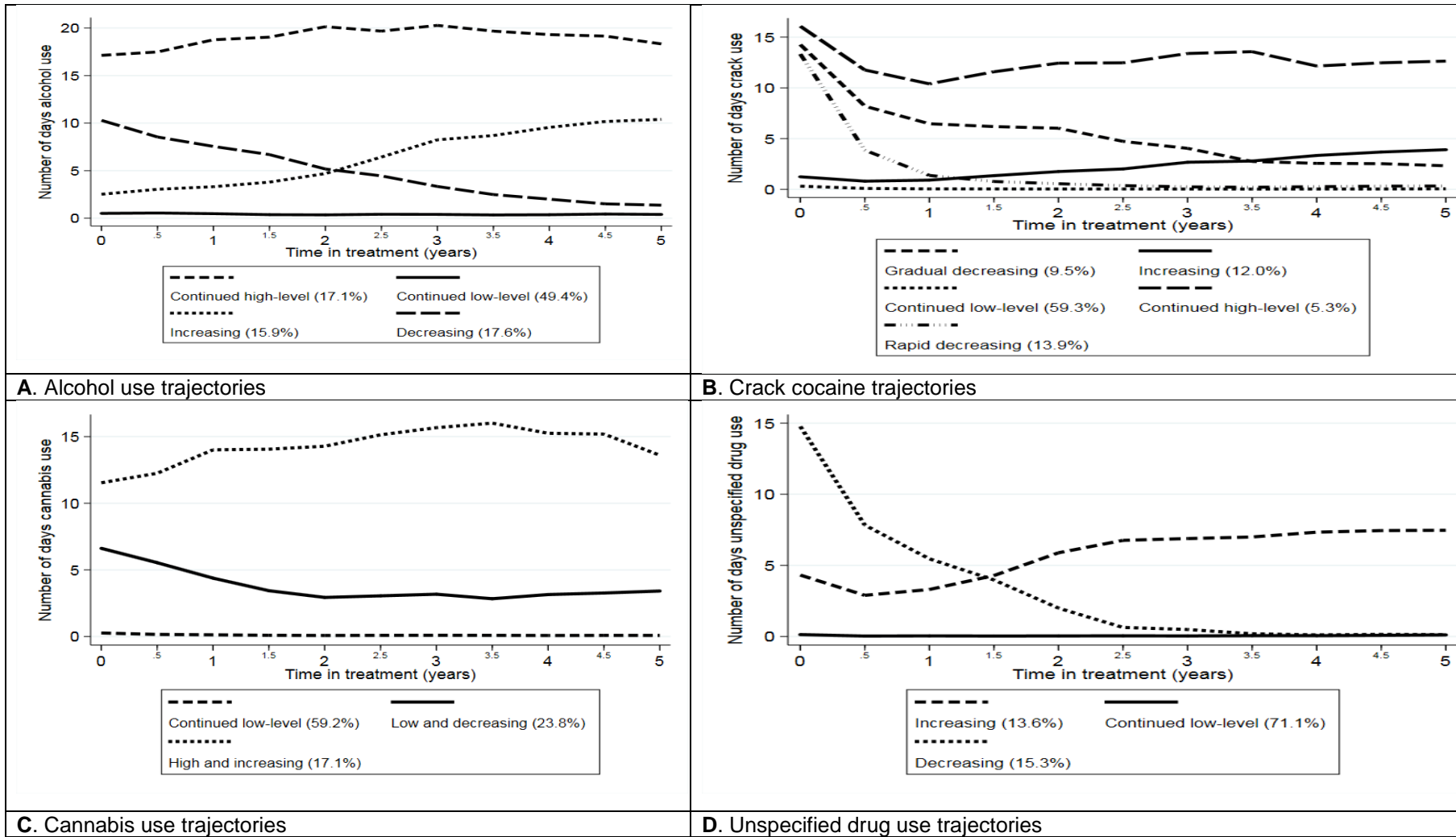


Figure 5.2 AOD trajectories over 5 years of continuous OST

5.5.4 AOD TRAJECTORIES REGRESSED ON HEROIN USE

The distribution of AOD trajectory groups within each of the heroin use trajectory classes is shown in **Table 5.3**. Relative risk ratios (RRR) and 95% confidence intervals (CI) from the multiply imputed multivariable multinomial regression analyses of the relationship between heroin and AOD use are displayed in **Tables 5.4-5.7**.

For brevity, we focused on the ‘rapid decreasing’ heroin class as the referent (Model 4, Tables 5.4-5.7). Members of the ‘continued high-level’ heroin use class were:

- more likely to be members of the ‘continued high-level’ alcohol class (21.7% vs 15.5%: RRR 1.24; 95% CI 1.01-1.53), and less likely to be members of the ‘decreasing’ alcohol use class (12.1% vs 20.4%: RRR 0.57; 95% CI 0.45-0.71);
- more likely to members of crack cocaine ‘continued high-level’ (23.7% vs 0.8%; RRR 58.66; 95% CI 34.23-100.54), ‘increasing’ (17.3% vs 4.5%; RRR 6.45; 95% CI 4.89-8.51), ‘gradual decreasing’ (10.9% vs 3.4%; RRR 5.65; 95% CI 4.09-7.79) classes, were less likely to be members of the ‘rapid decreasing’ class (8.9% vs 22.3%; RRR 0.66; 95% CI 0.52-0.84);
- less likely to be members of the ‘high and increasing’ cannabis group (11.0% vs 19.2%: RRR 0.49; 95% CI 0.39-0.62); and
- more likely to be members of the ‘increasing’ unspecified drug class (17.6% vs 9.7%: RRR 1.70; 95% CI 1.36-2.12).

Table 5.3 Alcohol and other drug use trajectory group membership conditional on heroin use trajectory group

AOD use trajectory groups	Heroin use trajectory					Total (n=7,659)
	Gradual decreasing (n=1,604)	Decreasing then increasing (n=1,659)	Continued low- level (n=1,298)	Rapid decreasing (n=1,957)	Continued high- level (n=1,141)	
Alcohol						
Continued high-level	283 (17.6)	284 (17.1)	197 (15.2) ^e	304 (15.5) ^e	247 (21.7) ^{c,d}	1315 (17.2)
Continued low-level ⁺	769 (47.9)	800 (48.2)	677 (52.2)	965 (49.3)	566 (49.6)	3777 (49.3)
Increasing	247 (15.4) ^c	312 (18.8) ^{c,d}	184 (14.2) ^{a,b,e}	288 (14.7) ^b	190 (16.7) ^c	1221 (15.9)
Decreasing	305 (19.0) ^e	263 (15.9) ^{d,e}	240 (18.5) ^e	400 (20.4) ^{b,e}	138 (12.1) ^{a,b,c,d}	1346 (17.6)
Crack cocaine						
Gradual decreasing	317 (19.8) ^{b,c,d,e}	197 (11.9) ^{a,c,d}	25 (1.9) ^{a,b,d,e}	67 (3.4) ^{a,b,c,e}	124 (10.9) ^{a,c,d}	730 (9.5)
Increasing	169 (10.5) ^{b,c,d,e}	368 (22.2) ^{a,c,d}	94 (7.2) ^{a,b,e}	87 (4.5) ^{a,b,e}	197 (17.3) ^{a,c,d}	915 (11.9)
Continued low-level ⁺	793 (49.4)	837 (50.5)	1107 (85.3)	1352 (69.1)	448 (39.3)	4537 (59.2)
Continued high-level	51 (3.2) ^{c,d,e}	64 (3.9) ^{c,d,e}	5 (0.4) ^{a,b,e}	15 (0.8) ^{a,b,e}	270 (23.7) ^{a,b,c,d}	405 (5.3)
Rapid decreasing	274 (17.1) ^{b,c,e}	193 (11.6) ^{a,c,d}	67 (5.2) ^{a,b,d,e}	436 (22.3) ^{b,c,e}	102 (8.9) ^{a,c,d}	1072 (14.0)
Cannabis						
Continued low-level ⁺	930 (58.0)	969 (58.4)	760 (58.6)	1133 (57.9)	737 (64.6)	4529 (59.1)
Low and decreasing	391 (24.4)	433 (26.1) ^{c,e}	271 (20.9) ^b	448 (22.9)	279 (24.5) ^b	1822 (23.8)
High and increasing	283 (17.6) ^e	257 (15.5) ^{c,e}	267 (20.6) ^{b,e}	376 (19.2) ^{b,e}	125 (11.0) ^{a,b,c,d}	1308 (17.1)
Unspecified drug						
Increasing	245 (15.3) ^{c,d}	248 (15.0) ^d	159 (12.3) ^{a,e}	189 (9.7) ^{a,b,e}	201 (17.6) ^{c,d}	1042 (13.6)
Continued low ⁺	1075 (67.0)	1189 (71.7)	934 (72.0)	1464 (74.8)	781 (68.5)	5443 (71.1)
Decreasing	284 (17.7) ^{b,e}	222 (13.4) ^a	205 (15.8)	304 (15.5)	159 (13.9) ^a	1174 (15.3)

Figures presented in table are number of participants (percentages)

⁺ Represents the base outcome in the from all-case, multiply imputed, multivariable multinomial logistic regression models

^{a,b,c,d,e} Represent significant statistical differences when different heroin use trajectory groups are used as referent categories (c.f. Supplementary Tables 1-4)

Table 5.4 Multiply imputed, multivariable, multinomial logistic regression models of alcohol trajectory group membership (n=7,717)

Alcohol trajectory group	Heroin trajectory group	Multinomial logistic regression model				
		Model 1 (Referent: Gradual decreasing heroin trajectory group)	Model 2 (Referent: Decreasing then increasing heroin trajectory group)	Model 3 (Referent: Continued low-level heroin trajectory group)	Model 4 (Referent: Rapid decreasing heroin trajectory group)	Model 5 (Referent: Continued high-level heroin trajectory group)
Continued high level	Gradual decreasing	-	1.02 (0.84,1.25)	1.24 (1.00,1.54)	1.08 (0.89,1.31)	0.87 (0.70,1.07)
	Decreasing then increasing	0.98 (0.80,1.19)	-	1.21 (0.98,1.50)	1.05 (0.87,1.28)	0.85 (0.69,1.04)
	Continued low-level	0.81 (0.65,1.00)	0.82 (0.66,1.02)	-	0.87 (0.70,1.07)	0.70 (0.56,0.88)
	Rapid decreasing	0.93 (0.76,1.12)	0.95 (0.78,1.15)	1.15 (0.93,1.42)	-	0.80 (0.65,0.99)
	Continued high-level	1.15 (0.94,1.42)	1.18 (0.96,1.45)	1.43 (1.14,1.80)	1.24 (1.01,1.53)	-
Increasing	Gradual decreasing	-	0.84 (0.69,1.02)	1.25 (1.00,1.56)	1.05 (0.86,1.28)	0.97 (0.78,1.21)
	Decreasing then increasing	1.19 (0.98,1.44)	-	1.48 (1.20,1.84)	1.25 (1.04,1.51)	1.15 (0.93,1.42)
	Continued low-level	0.80 (0.64,1.00)	0.67 (0.54,0.83)	-	0.84 (0.68,1.04)	0.78 (0.61,0.99)
	Rapid decreasing	0.95 (0.78,1.16)	0.80 (0.66,0.97)	1.19 (0.96,1.47)	-	0.92 (0.74,1.14)
	Continued high-level	1.03 (0.83,1.28)	0.87 (0.70,1.07)	1.29 (1.01,1.63)	1.08 (0.87,1.34)	-
Decreasing	Gradual decreasing	-	1.21 (1.00,1.47)	1.09 (0.89,1.34)	0.92 (0.77,1.10)	1.63 (1.29,2.05)
	Decreasing then increasing	0.83 (0.68,1.00)	-	0.90 (0.73,1.11)	0.76 (0.63,0.91)	1.35 (1.07,1.70)
	Continued low-level	0.92 (0.75,1.12)	1.11 (0.90,1.36)	-	0.84 (0.70,1.02)	1.49 (1.17,1.90)
	Rapid decreasing	1.09 (0.91,1.30)	1.31 (1.09,1.58)	1.19 (0.98,1.44)	-	1.77 (1.41,2.21)
	Continued high-level	0.61 (0.49,0.77)	0.74 (0.59,0.94)	0.67 (0.53,0.85)	0.57 (0.45,0.71)	-

Relative risk ratios for baseline covariates are not shown in Tables 5.4-5.7

Table 5.5 Multiply imputed, multivariable, multinomial logistic regression models of crack cocaine trajectory group membership (n=7,717)

		Multinomial logistic regression model				
Crack cocaine trajectory group	Heroin trajectory group	Model 1 (Referent: Gradual decreasing heroin trajectory group)	Model 2 (Referent: Decreasing then increasing heroin trajectory group)	Model 3 (Referent: Continued low-level heroin trajectory group)	Model 4 (Referent: Rapid decreasing heroin trajectory group)	Model 5 (Referent: Continued high-level heroin trajectory group)
Gradual decreasing	Gradual decreasing	-	1.65 (1.35,2.03)	18.59 (12.19,28.35)	8.10 (6.11,10.72)	1.43 (1.13,1.83)
	Decreasing then increasing	0.61 (0.49,0.74)	-	11.25 (7.32,17.29)	4.90 (3.65,6.57)	0.87 (0.67,1.12)
	Continued low-level	0.05 (0.04,0.08)	0.09 (0.06,0.14)	-	0.44 (0.27,0.70)	0.08 (0.05,0.12)
	Rapid decreasing	0.12 (0.09,0.16)	0.20 (0.15,0.27)	2.30 (1.44,3.67)	-	0.18 (0.13,0.24)
	Continued high-level	0.70 (0.55,0.89)	1.15 (0.89,1.49)	12.96 (8.27,20.33)	5.65 (4.09,7.79)	-
Increasing	Gradual decreasing	-	0.47 (0.38,0.58)	2.47 (1.88,3.24)	3.17 (2.41,4.16)	0.49 (0.39,0.62)
	Decreasing then increasing	2.11 (1.72,2.60)	-	5.21 (4.07,6.68)	6.69 (5.21,8.59)	1.04 (0.84,1.28)
	Continued low-level	0.41 (0.31,0.53)	0.19 (0.15,0.25)	-	1.28 (0.95,1.74)	0.20 (0.15,0.26)
	Rapid decreasing	0.32 (0.24,0.42)	0.15 (0.12,0.19)	0.78 (0.57,1.06)	-	0.16 (0.12,0.20)
	Continued high-level	2.04 (1.61,2.58)	0.96 (0.78,1.19)	5.02 (3.81,6.62)	6.45 (4.89,8.51)	-
Continued high level	Gradual decreasing	-	0.80 (0.54,1.17)	14.86 (5.88,37.58)	5.93 (3.30,10.66)	0.10 (0.07,0.14)
	Decreasing then increasing	1.25 (0.85,1.84)	-	18.63 (7.43,46.71)	7.43 (4.19,13.18)	0.13 (0.09,0.17)
	Continued low-level	0.07 (0.03,0.17)	0.05 (0.02,0.13)	-	0.40 (0.14,1.10)	0.01 (0.00,0.02)
	Rapid decreasing	0.17 (0.09,0.30)	0.13 (0.08,0.24)	2.51 (0.91,6.95)	-	0.02 (0.01,0.03)
	Continued high-level	9.9 (7.14,13.73)	7.89 (5.82,10.7)	147.10 (59.89,361.27)	58.66 (34.23,100.54)	-
Rapid decreasing	Gradual decreasing	-	1.47 (1.19,1.82)	5.60 (4.20,7.45)	1.02 (0.85,1.22)	1.55 (1.20,2.00)
	Decreasing then increasing	0.68 (0.55,0.84)	-	3.80 (2.83,5.11)	0.69 (0.57,0.84)	1.05 (0.80,1.37)
	Continued low-level	0.18 (0.13,0.24)	0.26 (0.20,0.35)	-	0.18 (0.14,0.24)	0.28 (0.20,0.39)
	Rapid decreasing	0.98 (0.82,1.17)	1.44 (1.19,1.75)	5.49 (4.18,7.21)	-	1.52 (1.19,1.94)
	Continued high-level	0.65 (0.50,0.84)	0.95 (0.73,1.24)	3.62 (2.60,5.05)	0.66 (0.52,0.84)	-

Table 5.6 Multiply imputed, multivariable, multinomial logistic regression models of cannabis trajectory group membership (n=7,717)

Cannabis trajectory group	Heroin trajectory group	Multinomial logistic regression model				
		Model 1 (Referent: Gradual decreasing heroin trajectory group)	Model 2 (Referent: Decreasing then increasing heroin trajectory group)	Model 3 (Referent: Continued low- level heroin trajectory group)	Model 4 (Referent: Rapid decreasing heroin trajectory group)	Model 5 (Referent: Continued high- level heroin trajectory group)
Low and decreasing	Gradual decreasing	-	0.94 (0.79,1.10)	1.13 (0.94,1.36)	1.00 (0.85,1.17)	1.15 (0.96,1.38)
	Decreasing then increasing	1.07 (0.91,1.26)	-	1.21 (1.01,1.45)	1.07 (0.91,1.25)	1.23 (1.03,1.47)
	Continued low-level	0.88 (0.73,1.06)	0.83 (0.69,0.99)	-	0.88 (0.74,1.05)	1.02 (0.83,1.24)
	Rapid decreasing	1.00 (0.85,1.18)	0.94 (0.80,1.10)	1.14 (0.95,1.36)	-	1.15 (0.96,1.38)
	Continued high-level	0.87 (0.72,1.04)	0.81 (0.68,0.97)	0.98 (0.80,1.20)	0.87 (0.72,1.04)	-
High and increasing	Gradual decreasing	-	1.17 (0.96,1.42)	0.90 (0.74,1.10)	0.88 (0.73,1.05)	1.79 (1.42,2.26)
	Decreasing then increasing	0.86 (0.70,1.04)	-	0.77 (0.63,0.94)	0.75 (0.63,0.90)	1.53 (1.21,1.94)
	Continued low-level	1.11 (0.91,1.36)	1.30 (1.06,1.59)	-	0.98 (0.81,1.18)	1.99 (1.56,2.54)
	Rapid decreasing	1.14 (0.95,1.36)	1.33 (1.11,1.60)	1.02 (0.85,1.23)	-	2.04 (1.62,2.56)
	Continued high-level	0.56 (0.44,0.71)	0.65 (0.52,0.83)	0.50 (0.39,0.64)	0.49 (0.39,0.62)	-

Table 5.7 Multiply imputed, multivariable, multinomial logistic regression models of other drug trajectory group membership (n=7,717)

Unspecified drug trajectory group	Heroin trajectory group	Multinomial logistic regression model				
		Model 1 (Referent: Gradual decreasing heroin trajectory group)	Model 2 (Referent: Decreasing then increasing heroin trajectory group)	Model 3 (Referent: Continued low- level heroin trajectory group)	Model 4 (Referent: Rapid decreasing heroin trajectory group)	Model 5 (Referent: Continued high- level heroin trajectory group)
Increasing	Gradual decreasing	-	1.06 (0.87,1.29)	1.27 (1.01,1.59)	1.58 (1.28,1.94)	0.93 (0.75,1.15)
	Decreasing then increasing	0.94 (0.78,1.15)	-	1.20 (0.96,1.49)	1.49 (1.21,1.83)	0.88 (0.71,1.08)
	Continued low-level	0.79 (0.63,0.99)	0.84 (0.67,1.04)	-	1.24 (0.99,1.57)	0.73 (0.58,0.93)
	Rapid decreasing	0.63 (0.51,0.78)	0.67 (0.55,0.82)	0.80 (0.64,1.01)	-	0.59 (0.47,0.73)
	Continued high-level	1.08 (0.87,1.33)	1.14 (0.93,1.41)	1.37 (1.08,1.73)	1.70 (1.36,2.12)	-
Decreasing	Gradual decreasing	-	1.39 (1.15,1.69)	1.18 (0.96,1.45)	1.19 (0.99,1.43)	1.33 (1.07,1.65)
	Decreasing then increasing	0.72 (0.59,0.87)	-	0.85 (0.68,1.05)	0.86 (0.71,1.04)	0.95 (0.76,1.19)
	Continued low-level	0.85 (0.69,1.04)	1.18 (0.95,1.46)	-	1.01 (0.83,1.24)	1.13 (0.89,1.42)
	Rapid decreasing	0.84 (0.70,1.01)	1.17 (0.96,1.41)	0.99 (0.81,1.21)	-	1.11 (0.90,1.38)
	Continued high-level	0.75 (0.61,0.94)	1.05 (0.84,1.31)	0.89 (0.70,1.12)	0.90 (0.73,1.11)	-

5.5.5 PROBABILITY OF MEMBERSHIP IN THE HEROIN USE TRAJECTORY GROUP

Table 5.8 shows the probability of membership in the heroin use trajectory group

conditional on AOD classes. Among patients classified as members of ‘decreasing’ alcohol use trajectory, 10% were members of ‘continued high-level’ heroin non-response class, and 30% were members of the ‘rapid decreasing’ heroin good response class.

In the ‘gradual decreasing’ crack cocaine use class, 43% were members of the ‘gradual decreasing’ heroin use class, and among ‘rapid decreasing’ crack cocaine group, 41% were members of ‘rapid decreasing’ heroin use class. Only 1% of the ‘continued high-level’ crack cocaine use group were members of the ‘continued low-level’ heroin use class while 67% of this non-responding crack cocaine class were in the ‘continued high-level’ heroin use class. For cannabis, only 10% of the patients in the ‘high and increasing’ class up were members of the ‘continued high-level’ heroin use class. For the unspecified drug, only 14% of the continued low-level class were members of the ‘continued high-level’ heroin class and 27% were in the ‘rapid decreasing’ heroin group.

5.5.6 TREATMENT STATUS AT THE END OF YEAR 7

At the end of Year 7, 4,615 (60.3%) were still enrolled in OST. During Year 6 and 7, 1,986 (25.9%) exited treatment unsuccessfully, and 1,058 (13.8%) successfully completed treatment. Among this group, 16.5% (n=175) were re-admitted to treatment in the next six months, five were incarcerated and one person died from opioid-related poisoning. The SCNR outcome was therefore achieved by 877 of 3,044 patients discharged from OST (28.8%) .

SCNR was most likely to be attained by the ‘rapid decreasing’ heroin class (39.7%). The ‘continued high-level’ heroin use trajectory group was least likely to achieve the SCNR (16.2%), followed by the ‘decreasing then increasing’ group (19.6%). The

‘continued low-level use’ and ‘gradual decreasing use’ groups had similar levels of SCNR (31.2% and 31.7%, respectively).

5.5.7 IMPACT OF AOD TRAJECTORY MEMBERSHIP ON OUTCOME

Table 5.9 shows the results of the multiply imputed, multivariable, multilevel logistic regression analyses. Within the ‘continued high-level’ heroin use class, patients with a ‘rapid decreasing’ crack cocaine trajectory had an increased likelihood of achieving SCNR (adjusted odds ratio [AOR] 1.70; 95% confidence interval [CI] 1.04-2.77). Membership of the ‘increasing’ unspecified drug class was associated with a decreased likelihood of achieving SCNR (AOR 0.47; 95% CI 0.27-0.81).

Among the ‘decreasing then increasing’ heroin trajectory group, a decreased likelihood of achieving SCNR was associated with ‘continued high-level’ alcohol use (AOR 0.43; 95% CI 0.21-0.88), ‘gradual decreasing’ crack use (AOR 0.42; 95% CI 0.18-0.96), ‘increasing’ crack use (AOR 0.50; 95% CI 0.27-0.93) and ‘low and decreasing’ cannabis use (AOR 0.50; 95% CI 0.28-0.92).

There was a decreased likelihood of achieving SCNR for patients in the ‘increasing’ crack cocaine class within the ‘gradual decreasing’ heroin use class (AOR 0.22; 95% CI 0.07-0.66) and an increased likelihood of achieving SCNR for patients in the ‘rapid decreasing’ heroin class who were members of the ‘low and decreasing’ cannabis class (AOR 2.39; 95% CI 1.29-4.40).

Table 5.8 Probability of heroin use trajectory group conditional on AOD use trajectory group

AOD use trajectory groups	Heroin use trajectory group					Total (n=7,659)
	Gradual decreasing (n=1,604)	Decreasing then increasing (n=1,659)	Continued low-level (n=1,298)	Rapid decreasing (n=1,957)	Continued high-level (n=1,141)	
Alcohol						
Continued high-level	283 (0.22)	284 (0.22)	197 (0.15)	304 (0.23)	247 (0.19)	1315 (1.00)
Continued low-level	769 (0.20)	800 (0.21)	677 (0.18)	965 (0.26)	566 (0.15)	3777 (1.00)
Increasing	247 (0.20)	312 (0.26)	184 (0.15)	288 (0.24)	190 (0.16)	1221 (1.00)
Decreasing	305 (0.23)	263 (0.20)	240 (0.18)	400 (0.30)	138 (0.10)	1346 (1.00)
Crack cocaine						
Gradual decreasing	317 (0.43)	197 (0.27)	25 (0.03)	67 (0.09)	124 (0.17)	730 (1.00)
Increasing	169 (0.18)	368 (0.40)	94 (0.10)	87 (0.10)	197 (0.22)	915 (1.00)
Continued low-level	793 (0.17)	837 (0.18)	1107 (0.24)	1352 (0.30)	448 (0.10)	4537 (1.00)
Continued high-level	51 (0.13)	64 (0.16)	5 (0.01)	15 (0.04)	270 (0.67)	405 (1.00)
Rapid decreasing	274 (0.26)	193 (0.18)	67 (0.06)	436 (0.41)	102 (0.10)	1072 (1.00)
Cannabis						
Continued low-level	930 (0.21)	969 (0.21)	760 (0.17)	1133 (0.25)	737 (0.16)	4529 (1.00)
Low and decreasing	391 (0.21)	433 (0.24)	271 (0.15)	448 (0.25)	279 (0.15)	1822 (1.00)
High and increasing	283 (0.22)	257 (0.20)	267 (0.20)	376 (0.29)	125 (0.10)	1308 (1.00)
Unspecified drug						
Increasing	245 (0.24)	248 (0.24)	159 (0.15)	189 (0.18)	201 (0.19)	1042 (1.00)
Continued low-level	1075 (0.20)	1189 (0.22)	934 (0.17)	1464 (0.27)	781 (0.14)	5443 (1.00)
Decreasing	284 (0.24)	222 (0.19)	205 (0.17)	304 (0.26)	159 (0.14)	1174 (1.00)

Table 5.9 Multiply imputed, multivariable, logistic regression models of SCNR outcome

AOD use trajectory groups	Heroin use trajectory				
	Continued high-level (n= 441; SCNR=16.2%)	Decreasing then increasing (n= 649; SCNR=19.6%)	Continued low-level (n= 504; SCNR=31.2%)	Gradual decreasing (n= 637; SCNR=31.7%)	Rapid decreasing (n= 813; SCNR=39.7%)
Alcohol					
Continued low-level	-	-	-	-	-
Continued high-level	0.47 (0.27,0.82)	0.43 (0.21,0.88)	0.66 (0.33,1.30)	0.75 (0.47,1.20)	1.29 (0.65,2.55)
Increasing	0.59 (0.34,1.01)	0.97 (0.53,1.76)	0.65 (0.34,1.23)	1.31 (0.82,2.08)	0.94 (0.43,2.08)
Decreasing	0.75 (0.46,1.22)	1.06 (0.57,1.97)	0.90 (0.51,1.59)	1.13 (0.76,1.69)	1.00 (0.42,2.39)
Crack cocaine					
Continued low-level	-	-	-	-	-
Gradual decreasing	0.98 (0.60,1.61)	0.42 (0.18,0.96)	0.22 (0.02,2.04)	0.49 (0.18,1.33)	1.15 (0.43,3.04)
Increasing	0.58 (0.29,1.16)	0.50 (0.27,0.93)	0.58 (0.23,1.44)	0.22 (0.07,0.66)	1.13 (0.53,2.41)
Continued high-level	1.18 (0.47,2.97)	0.86 (0.29,2.55)	- ^a	- ^b	1.23 (0.61,2.50)
Rapid decreasing	1.70 (1.04,2.77)	1.03 (0.54,1.97)	0.59 (0.20,1.77)	1.18 (0.81,1.71)	1.16 (0.41,3.30)
Cannabis					
Continued low-level	-	-	-	-	-
Low and decreasing	0.90 (0.57,1.43)	0.50 (0.28,0.92)	1.15 (0.68,1.95)	1.31 (0.90,1.90)	2.39 (1.29,4.40)
High and increasing	1.30 (0.80,2.12)	1.53 (0.84,2.76)	1.04 (0.59,1.83)	1.44 (0.96,2.17)	1.43 (0.59,3.42)
Unspecified drug					
Continued low-level	-	-	-	-	-
Increasing	0.47 (0.27,0.81)	1.04 (0.55,1.96)	0.70 (0.34,1.43)	0.88 (0.49,1.57)	0.97 (0.47,2.00)
Decreasing	0.84 (0.52,1.34)	1.28 (0.69,2.37)	1.02 (0.54,1.91)	0.70 (0.45,1.11)	0.92 (0.41,2.07)

Adjusted odds ratios for baseline covariates are not shown

^a There were only 3 patients from the 'continued low-level' heroin trajectory group who were also in the 'continued high-level' crack cocaine trajectory, and these were removed from analysis.^b There were only 5 patients from the 'gradual decreasing' heroin trajectory group who were also in the 'continued high-level' crack cocaine trajectory, and these were removed from analysis.

5.6 DISCUSSION

Over long-term continuous OST, we identified five trajectory classes for use of crack cocaine, four for alcohol, three for cannabis and three for unspecified drug use. In relation to our aims, each of these four substances contained an 'increasing' trajectory class. We found that the 'rapid decreasing' heroin trajectory group was less likely to be represented in both the 'increasing' crack cocaine and 'other drug' classes (although there was an increased likelihood of being represented in the 'high and increasing' cannabis use group). Membership of the 'increasing' crack cocaine class was associated with a decreased likelihood of achieving the study outcome measure for two of the five heroin classes, while membership of the 'increasing' unspecified drug class was also associated with a decreased likelihood of achieving the outcome, at least for the 'continued high-level' heroin trajectory group.

5.6.1 INTEGRATION WITH THE LITERATURE

Similar to other group based trajectory modelling studies (Grella and Lovinger, 2011; Teesson et al., 2017b), we identified a sub-population of OUD patients who do not report a substantial improvement in drug use. In our study, we demonstrate that these patients are also more likely to use crack cocaine and alcohol at a higher frequency than other subpopulations, and the pattern of alcohol and other drug use has a detectable and negative influence on eventual successful completion of treatment. Grella and Lovinger (2011) reported that their 'no decrease' group was more likely to be represented in the 'late-onset increase' of alcohol and other drug use while Teesson et al (2017) noted that their 'no decrease' trajectory group were more likely to live in unstable accommodation, to be imprisoned and to have injection-related health problems. Taken together, this

seems to indicate a subpopulation for whom multiple problems emerge across several domains.

The increased likelihood of ‘rapid decreasing’ and ‘continued low-level’ heroin trajectory groups being represented in the ‘high and increasing’ cannabis trajectory group may reflect the potential for use of cannabis to be associated with a pathway away from use of heroin during OST (Sifaneck and Kaplan, 1995). Daily cannabis use has also been associated with less severe heroin dependence, a lowered likelihood of daily heroin use and an increasing likelihood of never injecting heroin (Valdez et al., 2008). It is notable, however, that the increased use of cannabis in these two heroin groups did not confer any advantage in terms of completing OST successfully. If cannabis use does increase the likelihood of OUD recovery, it would be expected to be associated with treatment completion, though improved treatment outcomes have not been reported elsewhere (Budney et al., 2002; Epstein and Preston, 2003). While outside the scope of this paper, it is interesting to note the emerging evidence base of cannabinoid-opioid interactions within noradrenergic neural circuitry and the potential for cannabinoids to influence opioid withdrawal symptoms (Scavone et al., 2013).

5.6.2 STRENGTHS AND LIMITATIONS

A key study strength is the national, large-scale follow-up of all individuals accessing treatment for opioid use disorder in England and the utilisation of the national outcomes monitoring system to measure change in heroin and concurrent substance use throughout patients’ long-term enrolment in treatment. This ‘concurrent recovery monitoring’ system (McLellan et al., 2005) is a powerful platform for policy makers and researchers to efficiently evaluate the

effectiveness of community-based treatment under routine conditions. In addition, unlike other comprehensive administrative databases (Sahker et al., 2015; Stahler et al., 2016), the consent model supporting NDTMS enables linkage with subsequent treatment admissions to provide a measure of sustained recovery from OUD in patients exiting the treatment system.

Several limitations are also acknowledged: first, while the frequency of use is captured by the Treatment Outcomes Profile, NDTMS does not capture the quantity of heroin and other drugs being consumed. It is possible that analysis of composite frequency by quantity metrics would yield different substance use trajectories, or that the 'continued high-level' groups do in fact demonstrate improvements in terms of quantity consumed. Second, NDTMS is a 'core dataset' and does not capture several covariates that may affect trajectory membership, including treatment motivation (Simpson and Joe, 1993), engagement (Simpson et al., 1995) and other recovery strengths (Gossop et al., 2002d). Third, the observational design of this study does not allow inference of causality. It is not possible to determine whether low-level or reducing heroin use was caused by increased use of cannabis (or *vice versa*), or whether a complex set of causal factors are involved. Finally, it is unfortunate that illicit benzodiazepine use is not captured by the TOP. This remains an important clinical issue in the treatment of OUD and is reported by a sizeable minority in the English treatment system.

5.6.3 CLINICAL IMPLICATIONS

Findings from this study and earlier reports underscore the challenge for OST services to support engagement and recovery for patients with illicit OUD. If OST does not suppress a patient's heroin use to any clinically meaningful extent, then there is a likelihood that approximately 40% will use alcohol or crack cocaine at a

consistently high or increasing level and 1 in 7 will report increasing use of other unspecified drugs. Helping a patient with heroin and poly-substance use may be very challenging, but this should be a high priority because of immediate health needs and because the success of OST is diminished. Screening for AOD use is recommended at treatment admission and at regular clinical reviews, which can be a rapid assessment (Ali et al., 2013), and the assessment of other important aspects of personal and social functioning should not be overlooked (Marsden et al., 2014).

If there is an unsatisfactory response to flexible dosing, it may be appropriate to suggest a change in medication (e.g. switching from methadone to buprenorphine), reinstate supervised administration (Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group, 2017), or offer a targeted psychosocial intervention for opioids (Marsden et al., 2017), alcohol (Nolan et al., 2016) or cocaine (Marsden et al., 2018a) from the service if there are resources or by referral. Although it may be discouraging that some patients continue to alcohol and other drugs, treatment may still offer provide important harm reduction benefits by reducing the risk of opioid poisoning (Cornish et al., 2010; White et al., 2015) and, taking a wider societal perspective, there is an overall economic benefit-cost ratio from investing in OST (Zarkin et al., 2005).

5.6.4 CONCLUSIONS

This study highlights the importance of concurrent monitoring of adjunctive substance use in the treatment of opioid use disorder as a sizeable minority of patients either increase or maintain a high level of concurrent drug use and increasing drug use trajectories have a negative impact on positive outcome.

These findings reinforce the conception of OUD as a complex and chronic condition. The next task for our research group is to examine the longitudinal inter-relationship between substance use, employment and housing.

Chapter 6 DISCUSSION OF THESIS

6.1 SUMMARY OF MAIN FINDINGS

This thesis has been structured around findings from three interconnected studies on an English national prospective cohort of adults who have been treated for OUD. All of them use administrative data and multivariable, longitudinal statistical procedures to investigate the effectiveness of treatment. During the course of my doctoral studies, each of these three studies was reported and published as a research article in one of the leading peer reviewed addictions scientific journals (*Drug and Alcohol Dependence*).

Study 1 demonstrated that patients presenting with OUD are far from homogeneous, that sub-populations can be identified at the start of treatment and that these sub-populations do not all share the same likelihood of completing treatment successfully. I showed that Latent Class Analysis can be used to identify different groups of heroin users. In addition, those heroin users who also report a concurrent crack cocaine disorder are less likely to complete treatment successfully within five years. Spending at least two years in treatment increased the likelihood of completing treatment successfully. In contrast, I demonstrate that being a current injector, being referred to treatment from the criminal justice system or having a history of previous treatment decreased the likelihood of completing treatment successfully.

Study 2 extended the evidence base of longitudinal sub-populations in OUD patients by demonstrating that different trajectory groups can be identified in national administrative databases and that they are predictive of subsequent successful completion of treatment. I used Latent Class Growth Analysis to

identify five distinct groups of heroin users based on their response to treatment and concluded that those least responsive in terms of reducing heroin using days were also those least likely to subsequently recover.

Study 3 demonstrated the importance for clinicians, researchers and policy makers to ensure due diligence is paid not only to the changes in the primary problematic substance during treatment – heroin in this case – but also to that of other highly prevalent substances in the OUD population. I showed that these adjunctive substance use trajectories mitigated positive treatment outcomes. This study also utilised Latent Class Growth Analysis and showed that those heroin users least likely to reduce their frequency of heroin use were generally the same individuals that were consistently reporting high levels of crack cocaine use. Of particular note is the finding that of individuals who had been considered members of a positive response heroin use trajectory in Study 2 (i.e. their heroin use was described as ‘gradual decreasing’ and this group was more than twice as likely to achieve the distal outcome), around one in ten were also on an ‘increasing’ crack cocaine trajectory and this severely hampered their likelihood of success.

All of these findings have implications for all levels of stakeholders who seek to increase the effectiveness of treatment and promote recovery from substance use disorders, be they keyworkers, service managers, treatment purchasers or government officials responsible for the effective delivery of treatment services. On this basis, it is reasonable to conclude that the National Drug Treatment Monitoring System, while imperfect, is a valuable resource to researchers working in this field, providing a rich source of cross-sectional and longitudinal data.

6.2 INTEGRATION AND IMPLICATIONS OF FINDINGS

6.2.1 UNSUCCESSFUL TREATMENT COMPLETION

Before turning to those patients whose frequency of heroin use did not substantially reduce over the time spent enrolled in treatment, it is important to recognise the considerable proportion of patients who prematurely disengaged from OUD treatment. Within the NDTMS lexicon, 'unsuccessful completions' (a collective term for those patients who died, were imprisoned, had an unsuccessful transfer or dropped out from treatment) accounted for 72.2% of patients discharged within the first five years of treatment as reported in Study 1.

6.2.1.1 FACTORS ASSOCIATED WITH UNSUCCESSFUL COMPLETIONS

There have been several reviews of dropout over the past forty years (Baekeland and Lundwall, 1975; Craig, 1985; Stark, 1992; Brorson et al., 2013b). These reviews consistently report that younger people are more likely to drop out of treatment, which aligns with the findings from Study 1 and Study 2 that older people were more likely to successfully complete treatment. The literature on drop out also points to gender being an inconsistent factor. In Study 1, males were less likely to successfully complete treatment while in Study 2 this effect was no longer observed.

Other important patient-level covariates in Study 1 included being homeless, from an area with higher deprivation, having a history of injecting, being referred to treatment from the criminal justice system, having a history of previous treatment and a longer heroin using career. These were all negative factors in recovery. Conversely being employed at the start of treatment was a positive factor. In Study 2, where patients had already been in treatment for a full five years and successful completion of treatment was measured in Year 6 and Year 7, being

employed at the start of treatment demonstrated an increased likelihood of eventual recovery. Consistent with Study 1, a history of injecting and a longer heroin using career were associated with a decreased likelihood of eventual recovery.

It is interesting to note that unlike other large-scale studies on treatment completion (Arndt et al., 2013; Mennis and Stahler, 2016), the adjusted models reported in Study 1 and Study 2 did not find an association between patients from black and minority ethnicities (BME) and the likelihood of recovery. It is possible that this reflects a socio-cultural difference in the relationship of BME status and heroin use between the UK and North America in that BME status in the UK is associated with a lower likelihood of involvement with heroin. The model results did, however, find some general support for the construct of 'physical capital' (Cloud and Granfield, 2008), in that homelessness was a negative predictor of recovery in Study 1 while employment was a positive predictor in Study 1 and Study 2.

Given the consistent positive finding surrounding employment, and in the context of relatively few patients being employed when first admitted to treatment (12.5%), it is encouraging that Public Health England are currently conducting an RCT to evaluate the impact of Individual Placement and Support (IPS; Drake et al., 2012) in securing gainful employment for patients currently accessing treatment. IPS has been shown to increase the employment rate in people with severe mental health illness (Marshall et al., 2014). In a recent pilot study of individuals receiving methadone treatment, 50% of those assigned to IPS gained a job within one year compared with 22% of the control group (Lones et al., 2017). Public Health England will seek to establish whether or not these gains

hold true in a large multi-site study and whether or not other benefits, such as reduced criminal offending or hospital resource utilisation, can be detected.

Also of note in Study 1 is the finding that increased time spent engaged in treatment is associated with an increased likelihood of successful completion. This aligns with other large-scale studies (Hubbard et al., 2003; Simpson and Sells, 1990) and is highly suggestive that OUD treatment should not be time-limited (Advisory Council on the Misuse of Drugs, 2014).

After controlling for patient-level and local area-level social deprivation predictors associated with outcome, the analysis indicated that local treatment systems with a high rate of unsuccessful completions are also those same systems with a much larger opiate using population. Likely to be interlinked with this higher prevalence rate, these systems also have a higher rate of offending and a higher rate of drug-related deaths. This finding suggests that there is some form of social network influence in operation.

A person's social network is made up of those individuals with whom, to a greater to lesser degree, the person is socially acquainted. Social selection theory contends that a drug user would switch social networks in order to be able to spend more time with other drug users while social influence theory suggests that a person observing drug taking behaviour within their own network be would more likely to take drugs and so behave more like their friends (Dohrenwend et al., 1992).

Social networks can influence the transition to injecting as well as the decision to share injecting equipment (De et al., 2007; Neaigus et al., 2006). In addition,

living with a heroin user is predictive of patients continuing to use illicit opioids (Gogineni et al., 2001; Lions et al., 2014). The availability of drugs is often cited as a reason for occasional use (Best et al., 1999), and heroin users who have achieved abstinence often cite moving away from a drug-using social network and towards a non-using network as a contributory factor to overcoming dependence (Best et al., 2008; Buchanan and Latkin, 2008).

By utilising structural equation modelling, it is possible to simultaneously estimate the direction of influence over time – i.e. does drug using behaviour lead towards drug-using friends (social selection) or do drug-using friends lead towards drug using (social influence)? In a study of more than 1,100 adults with a lifetime history of heroin and/or cocaine use, Bohnert et al. (2009) found evidence for both forms of influence, but noted that most changes in drug use over time were due to changes in the make-up of the social network rather than changes in friends' behaviour. Similar evidence for both social selection and social influence has been found in terms of alcohol consumption, with the researchers concluding that social selection effect appears to exert a stronger effect than social influence (Bullers et al., 2001). Changing the composition of social networks to include more non-users and fewer users is associated with a reduction in the risk of using opioids (Lions et al., 2014) and of engaging in risky injecting behaviour (Costenbader et al., 2006). Avoiding other drugs users limits the availability of the drug and also serves to reduce exposure to drug conditioned stimuli and social pressure to use (Havassy et al., 1995).

Interventions such as Social Behaviour and Network Therapy (SBNT) are aimed at improving the social support for heroin addicts by involving close friends and family as part of the treatment process. A recent pilot study in England, however,

found that while drug workers could be trained to a satisfactory level in administering the intervention, it was difficult to engage patients in this form of psychosocial intervention. Only 31% of those assigned to a brief version of SBNT arm of the trial completed all four sessions (Day et al., 2018). Overall, no statistically significant difference in illicit heroin was found between SBNT and treatment as usual.

6.2.1.2 MORTALITY

6.2.1.2.1 DRUG-RELATED POISONING MORTALITY

The smallest of the NDTMS unsuccessful completion categories – patients who died (n=684; 1.5% of discharges within five years) – is arguably the most important. It should be noted at the outset that large scale treatment provision has been estimated to prevent around 900 opioid-related poisonings in England each year (White et al., 2015) and it is likely that the number of deaths would have been higher in the absence of treatment.

While the cause of mortality is not recorded on NDTMS, other research in England suggests that around 40% suffered a fatal drug poisoning (Pierce et al., 2015a). Recent national guidelines emphasise the importance of providing take home naloxone to mitigate the risk of a fatal opioid overdose (Public Health England, 2017b). Naloxone is an opioid antagonist and works by rapidly removing other molecules, such as heroin, from the mu-opioid receptors in the brain, thereby reversing respiratory depression. Through this action, timely administration of naloxone can avert a potentially fatal overdose. Guidelines recommend that naloxone is issued not only to the patient themselves, but to any individual needing access to it. The latter include the carers, family members or friends who may be liable to witness an overdose and, possibly, individuals in a

hostel or other facility where drug users gather and may be at risk (Public Health England, 2017b).

While monitoring the dispensing of naloxone within NDTMS is a welcome step forward, PHE does not as yet report the level of naloxone provision as part of their annual statistics (Public Health England, 2018a). Nonetheless, a recent PHE response to a freedom of information request reported that there were 15,279 individuals in treatment in 2017/18 who received at least one dose of take-home naloxone. There were 141,189 individuals accessing treatment for OUD in 2017/18, which means that around 11% of individuals at risk – and in contact with the treatment system – received this potentially lifesaving medication. In the context of continued growth in fatal drug-related poisonings in England, it is critically important that local treatment systems ensure that all patients engaging with the treatment system for OUD are provided with take-home naloxone and that they and any close friends or family are afforded training in its use.

It must be noted, however, that simply providing naloxone will not eliminate all instances of fatal opioid poisoning. Because a person experiencing an overdose is not capable of administering the antidote themselves, there must be another person present to administer the drug. Between 1997 and 2000 in San Francisco, for example, it was reported that almost 70% of those suffering from a fatal heroin-related overdose were alone at the time (Davidson et al., 2003). More recently, an investigation into 115 coroners' reports of drug-related deaths in England between 2014 and 2015 showed that 46 (40%) were alone at the time of death (Office for National Statistics, 2018b). Alongside the provision of naloxone, therefore, the harm reduction messaging of 'never use alone' needs to be promoted (Wojcicki, 2019).

6.2.1.2.2 OTHER CAUSE MORTALITY

If one makes the assumption that 40% of the deaths recorded on NDTMS are fatal drug poisonings, 60% die from other causes. In a large scale linkage study between NDTMS and the national administrative database on mortality, Pierce et al (2015) reported on the standardised mortality rate (SMR) for different causes of mortality in opioid users. The SMR is a useful summary of mortality risk in that it relates the expected number of deaths to those observed for the given set of gender and age. An SMR over one indicates an increased risk. The highest other cause SMR in this study was for viral hepatitis at 57.2, indicating that opioid users are 57 times more at risk of dying from hepatitis than the general population. Testing for, and treating, viral hepatitis should be a priority, and aligns with the World Health Organization's goal of eliminating viral hepatitis by 2030 (World Health Organization, 2017).

Other leading causes of death highlighted by Pierce et al (2015) include diseases relating to injections via the skin and subcutaneous tissue (SMR 17.2), chronic lower respiratory diseases (SMR 12.8), infectious/parasitic diseases (SMR 12.6) and liver cancer (SMR 9.2). A more recent study based in South London also reported that around 60% of excess deaths were not due to drug-related causes (Lewer et al., 2019). Instead, digestive diseases, respiratory diseases and external causes were the most common of the ICD-10 chapters and the largest subcategories were for liver disease, chronic obstructive pulmonary disease and accidents. Given the scope of diseases putting opioid users at heightened risk of death, this is yet another reason for ensuring all heroin users have appropriate access to General Practitioners. Regular linkage studies between NDTMS and the General Mortality Register held by the Office for National Statistics would

enable national administrators and researchers to monitor progress in this important area.

Another key area of concern is the prevalence of tobacco smoking in the OUD population. In Australia, almost 85% of patients attending methadone clinics reported tobacco smoking (Bowman et al., 2012), while in Mexico around 90% of people who inject drugs (PWID) reported tobacco smoking (Shin et al., 2013) and almost all (97%) of patients attending methadone or buprenorphine treatment in Italy reported tobacco smoking (Pajusco et al., 2012). In England, 68% of those starting treatment for OUD in 2017/18 reporting tobacco smoking, more than four times the rate of the general adult population (Public Health England, 2018a). This national figure masks geographic and setting variation: 97% of drug users in an in-patient setting in England reported tobacco smoking (Harris et al., 2000) and 88% of patients accessing a community treatment service in London reported tobacco smoking (Cookson et al., 2014).

Tobacco smoking behaviour is important because persons with OUD face a higher risk death from at least 19 tobacco-related conditions, with these conditions accounting for around 40% of deaths in this group (Callaghan et al., 2018). Yet the proportion of OUD smokers being referred for tobacco cessation services is minuscule. In England it is 3% (Public Health England, 2018a) and this is despite evidence that 40% of patients accessing drug treatment who smoke tobacco are motivated to quit immediately (Cookson et al., 2014). The frequency of tobacco smoking was added to the Treatment Outcomes Profile in 2016, which was unfortunately outside the timeframe of the studies reported here and could not be considered in Study 3 in particular.

6.2.1.3 IMPRISONMENT

The next largest category of unsuccessful discharges in Study 1 was for patients who were imprisoned (n=7,425; 16.0% of discharges). There is little community-based treatment providers can do in this scenario. An individual arrested and subsequently imprisoned will almost certainly undergo at least one healthcare assessment at the point of imprisonment and may have already been drug-tested by the police. Treatment is available in prisons but often requires the individual to declare their problem and consent to treatment. In 206/17, 29,626 individuals were treated for OUD while in prison (Public Health England, 2017c).

6.2.1.4 UNSUCCESSFUL TRANSFERS

Almost one in five of all patients who exited the treatment system within the first five years did so with the discharge status of 'unsuccessful transfer' (n=8,385; 18.1%). Within NDTMS, this discharge status entails an active referral by one specialist treatment service to another and yet the patient was not picked up by the receiving service within three weeks. There are a number of reasons why a patient may have failed to present at the subsequent treatment service. It may be that the next service does not submit records to NDTMS and therefore it is simply not possible to continue the administrative record of their ongoing treatment. Such a situation would emerge if a patient managed to secure funding to attend a private residential rehab or if a patient was transferred entirely to the care of a General Practitioner. It is also possible that, following the onward referral, a patient was imprisoned and this information was not available at the time the referring treatment service discharged the patient and submitted their NDTMS record. Possibly, the patient did not fully agree with the decision to move on to another service or was faced with practical barriers to engage with the next service, such as a greater travel distance or additional expense.

Whatever the reason, ‘unsuccessful transfers’ represent a substantial number of patients who are being failed by the referral pathway. As they are no longer receiving treatment, these patients are placed at a heightened risk of a fatal overdose. A recent examination of deaths following an ‘unsuccessful transfer’ in London revealed that such a discharge code results in excessive fatal overdose in the month immediately following the transfer, highlighting the crucial importance of ensuring such patients are picked up by the receiving treatment provider (Bogdanowicz et al., 2018).

Treatment services need to work more closely together to ensure the referred patient is actually received by the next service and, if not, to actively seek to re-engage the patient at the original treatment service. It is unfortunate that Public Health England do not provide information to the referring service about whether or not specific patients have successfully engaged with the service they have been referred to. While the referring service may make contact with the next service, this lack of data sharing on an ongoing and routine basis may unnecessarily be hampering the successful and safe flow of patients through the treatment system.

6.2.1.5 DROPOUTS

The largest category of ‘unsuccessful discharges’ is that of dropouts, consisting of 36% (n=16,613) of those exiting the treatment system in the first five years. While it is plausible that ‘drop outs’ are less motivated to continue with treatment compared with unsuccessful transfers, it is interesting to note that a higher proportion of those dropping out re-engage within six months than those with an unsuccessful transfer (35% cf. 28%). It is important that treatment services attempt to understand why they face such high levels of discharge and whether

or not the service being provided needs to change to better suit the needs of their patients.

6.2.1.6 RE-ENGAGEMENT

For patients who drop out of treatment, proactive and early re-engagement is recommended and services are encouraged to have effective re-engagement pathways in place (Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group, 2017). The results from Study 1 indicate that re-engagement should also be a priority for at least 54% of the English treatment population (i.e. those who drop out or are unsuccessfully transferred). One potential framework designed for this purpose is Recovery Management Checkups (RMC; Scott and Dennis, 2003). RMC is a multi-component processing that involves tracking (i.e. maintaining contact with patients), assessment (i.e. to determine whether patients have re-engaged in substance misuse), linkage (i.e. referrals to treatment), engagement (i.e. to ensure entry to treatment is as simple as possible) and retention (i.e. to encourage patients to stay in treatment for a defined amount of time). The RMC strategy up of ongoing assessment and early re-intervention appears to be effective.

A randomised controlled trial of 446 adults over a four-year period involved randomising half the participants to receive quarterly assessments plus RMC and the other half to the control condition of quarterly assessments only (Dennis and Scott, 2012). Participants in the RMC condition were more likely to return to treatment (70% cf. 51%), were faster to return to treatment (13 cf. 45 months), experienced fewer quarters in need of treatment (7.6 cf. 8.9) and reported more

days abstinent from alcohol and other drugs (70 cf. 63 out of 90 days at the last observation).

It would seem prudent for a similar RCT to be conducted in England in view of the large proportion of patients either dropping out of treatment (36%) or being unsuccessfully transferred for further treatment (18%). While these two premature discharge reasons may be a logical set of inclusion criteria, it would be unwise to ignore those patients who had successfully completed treatment (29% of those discharged) as almost a quarter of these (23.7%) were re-admitted of their own accord within six months of exit. The single most important metric adopted by Public Health England specifically defines recovery as a successful completion without re-admission within six months (Public Health England, 2015a) and re-engaging patients who have successfully completed treatment shortly after their exit would reduce the proportion achieving this key metric. Nonetheless, it would be unethical to ignore a group of patients who may be in need of treatment simply because it did not fit neatly within a bureaucratic worldview, particularly as those with a planned discontinuation of OST appear to be at a heightened risk of fatal overdose following termination of treatment (Bogdanowicz et al., 2018). Funding an impartial third party to conduct a multi-site RCT of RMC for all discharged patients would mitigate against the inherent conflict of interest.

6.2.2 CONTINUED USE OF ILLICIT OPIOIDS

Study 2 was an in-depth examination of self-reported heroin use frequency in those patients who had been continuously engaged in treatment for a five year period. A notable finding was that between Years 3 and 5 around 40% of the patients continued to report illicit opioid use, underscoring the challenges faced

by treatment providers to support patient engagement and recovery. It is important to remember that these patients were actively in receipt of OST and it is therefore appropriate to ask whether or not the treatment system is adequately addressing this level of continued use. One factor for improving this outcome is the prescribed medication dose, which can be easily changed.

When the first network of treatment clinics opened in England in 1968, it quickly became clear that there was a tension between patients accessing the service and the doctors responsible for their treatment. Patients had a vested interest in securing a prescription dose that met their needs while doctors had a duty to ensure the prescription was not so generous as to allow diversion to the black market. A game of 'cat and mouse' emerged, with some doctors assuming that whatever level of dose was requested, it should be reduced by half (Stimson and Oppenheimer, 1982). Some patients, for their part, were reported to target newly appointed doctors with perhaps exaggerated claims of withdrawal symptoms, or lost prescriptions, in the hope of gaining an increased dose. The perception of treatment clinics as places in which to receive one's desired drugs was not necessarily confined to patients – one doctor referred a patient to the regional 'drug abundance clinic' in Manchester in the early 1980s (Strang, 1984).

In many ways, this 'game' has continued since then. Current clinical guidelines place the therapeutic dose of methadone between 60-120mg per day (Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group, 2017) but national surveys have consistently found that more than half of patients receiving methadone or buprenorphine are being prescribed doses below the lower end of the recommended dose range (Strang et al., 2005, 1996). The dose received by patients is important in terms of suppressing illicit

opioid use. Patients who receive a low dose (20mg per day) are unlikely to demonstrate any reductions in illicit use (Strain et al., 1993), and patients receiving a dose in the therapeutic range (80-100mg per day) are more likely to test negative for illicit opioids than those receiving a lower (40-50mg per day) dose (Strain et al., 1999). A Cochrane review of the methadone dose-response confirmed that patients prescribed 60-100mg per day are more likely to be retained in treatment and to reduce illicit heroin and cocaine while in treatment (Faggiano et al., 2003).

Nonetheless, around a quarter of patients in England consider the dose they receive to be 'poor or bad' (Advisory Council on the Misuse of Drugs, 2015). Similarly, in the US, around a quarter of patients receive methadone doses too low to be effective (D'Aunno et al., 2014). The median dose of methadone prescribed by general practitioners in England increased between 1995 and 2005 from 40mg to 50mg (Strang et al., 2007) indicating that, even after a decade of recommendations of the greater benefit from daily doses in the 60-120mg dose range, at least half of patients in receipt of methadone are receiving a suboptimal dose.

Given the known importance of medication dose, it is unfortunate that NDTMS does not capture this information. NDTMS clearly needs to be enhanced to incorporate information on dose. The purpose of this is twofold. First, incorporation of dose would enable the estimation of whether or not, and to what degree, suboptimal dosing is associated with continued use of illicit heroin on top of that dose. When oral methadone is optimised (often considered to be ≥ 80 mg), it can lead to improved outcomes even in those who may be considered persistent treatment non-responders (Strang et al., 2010). Second, it would

provide the data required to monitor the degree to which extreme methadone prescribing practices may be occurring. Given the relationship between extreme methadone dose and the risk of methadone-specific mortality (Gao et al., 2016; Pierce et al., 2018), it is important for national administrators, treatment commissioners, managers and keyworkers to be aware of the extent of such practice and take appropriate action where necessary. It is encouraging that, at the time of writing, PHE is in the process of consulting on the next iteration of NDTMS. It remains to be seen whether or not dose will be incorporated.

6.2.3 SUSTAINED NON-RESPONSE

Study 2 highlighted the importance of research analytical methods to delineate longitudinal heroin use trajectories. Of particular concern are the 15% of patients who demonstrate sustained non-response over significant periods of time. This group of patients showed a rapid reduction in illicit heroin use within the first six months of treatment, but continued to report illicit use on about half the available days until the end of the observation period. While continued use of illicit opioids on top of an opioid prescription is a recognised problem (Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group, 2017), it is important for clinicians to identify non-response or deterioration at an early stage and to optimise treatment where possible. This could include, for example, splitting the dose into smaller daily doses, increasing the dose, reintroducing supervised consumption or offering a change in prescribed medication.

Study 2 found that psychosocial interventions, while being received by most but not all patients (92%), increased the likelihood of sustaining recovery and

underscored the importance of the adjunctive psychosocial component of treatment to enhance clinical benefit.

Attention to alcohol and other drug use is also important. Study 3 revealed that almost a quarter of patients in the 'continued high-level' heroin use trajectory were also on the 'continued high-level' crack cocaine use trajectory. Looked at another way, of those in this particular crack cocaine trajectory, 67% came from the 'continued high-level' heroin group. What this demonstrates is that those individuals who can be considered non-responders in terms of their heroin use are also often the same individuals who can be considered non-responders in terms of their crack cocaine use. Treating an OUD patient who has an ongoing concurrent crack cocaine problem, or any poly-drug use for that matter, may add to the difficulty and challenge, but it should be considered a high priority given the disparate health needs they engender and the negative impact they represent for OUD outcomes. It may be appropriate to offer targeted psychosocial interventions for opioids (Marsden et al., 2017), alcohol (Nolan et al., 2016) or cocaine (Marsden et al., 2018b).

It is important to note that, over the five-year observation period, any given patient may have seen up to three different treatment providing organisations – even while receiving treatment at the same location. This is because, in England, treatment commissioning has moved to being often re-commissioned on a three-year cycle. A patient may start treatment with one organisation, which is decommissioned at the end of Year 1 when a new provider is awarded the contract. This provider may subsequently be decommissioned at the end of Year 4 and so the patient is transferred to the care of yet another provider. A patient might be involved with more than three organisations, as was the case when

Lifeline (a provider organisation in England) initially secured many new contracts by offering low costs, subsequently became financially non-viable and collapsed. New arrangements for the patients under their care had to be urgently considered. This kind of systemic reorganisation may hinder the progress being made by patients as resources need to be redirected from clinical 'front line' work towards work required for tendering for new contracts (Day et al., 2018).

It should also be noted that, from the late 2000s onwards, around the time when patients selected for inclusion in the three studies of this thesis began treatment, there was an apparent shift in the behaviour of third-sector organisations. As outlined by Kalk et al (2018), instead of collaborating with existent NHS services, the third sector began to successfully bid to take over those same services. This change, coupled with budget cuts, has led to a reduction in funding to addiction services of around 30-50% and may have led to a situation where services with less qualified or experience staff are awarded contracts (Drummond, 2017; Kalk et al., 2018). This has been criticised as a move to 'survival of the cheapest'. It has been claimed, for example, that specialist addiction psychiatrists and nurses have been replaced, respectively, by sessional GPs and drug workers lacking specialist qualifications in order to drive costs down (Mohammadi, 2014).

Apart from facing changes in organisational philosophies and treatment policies, a patient may also be faced with having to develop a therapeutic relationship with a new clinician. From a clinician's perspective, aside from facing increased caseloads due to funding cuts – thereby managing the care of more patients with less time (The Guardian, 2017) – it is possible the information held on the patient's treatment history is not transferred over, making it difficult if not

impossible for the clinician to readily understand the progress a patient has made (or not) to date.

Commissioners should consider building into their contracts a requirement to ensure all patient-level data are properly transferred to a new treatment provider in those instances where a different organisation assumes the care of patients under a new contract. Any software utilised to submit data to NDTMS should have the in-built capability to enable for clinicians to track the long-term pattern of behaviour for any of the patients they are responsible for. Furthermore, national drug treatment administrators should make available performance monitoring reports focused on the long-term use of illicit opioids and adjunctive substances for managers and commissioners of services. This should be relatively simple to implement and could aid local planning and resource allocation and potentially improve outcomes in this important domain.

6.2.4 DETERIORATING HEROIN USE

Also requiring further consideration is the group of approximately 20% of patients who, following initial improvements in their illicit heroin use, exhibited a tendency to deteriorate after three years of treatment. Heroin addiction is a complex disorder and it is unsurprising that a proportion of patients in treatment take retrograde steps on their journey towards recovery. The challenge for professionals involved in the treatment of the disorder is to be responsive to such changes. Measurement-based care (MBC) is an evidence-based approach in which symptoms, such as self-reported illicit heroin use, are used to inform clinical practice. Various tools have been suggested for delivering MBC, including the Treatment Outcomes Profile (Marsden et al., 2008), the Addiction Dimensions for Assessment and Personalised Treatment (Marsden et al., 2014), the Brief

Addiction Monitor (Cacciola et al., 2013; Nelson et al., 2014) and the DSM-5 assessment for OUD (Marsden et al., 2019a). Whatever tool is deemed appropriate in a given setting, it is important that clinicians are responsive to changes reported by the patient. For example, by engaging with those patients whose illicit heroin use is increasing during treatment, it would be possible to offer changes to the OST drug or dose. Further, adoption of MBC can benefit the professional development of the clinician and lead to quality improvements in the treatment provider (Fortney et al., 2017).

6.2.5 SUSTAINED POSITIVE RESPONSE

Three other trajectory groups emerged from Study 2 and merit further discussion:

- (1) the 'continued low-level' group initiated OST while reporting close to zero days of illicit heroin use in the 28-days prior to admission and continued to follow this pattern of heroin use throughout the five years they spent in OST;
- (2) the 'rapid decreasing' group had substantial reductions within the first six-month period, with their monthly heroin use falling from 25 days to 5 days, continued to improve and maintained an abstinent state between Year 2 and Year 5;
- (3) the 'gradual decreasing' group took longer to achieve abstinence, getting there at the Year 5 mark.

These results indicate that abstaining from illicit heroin can be a lengthy process but it is achievable while engaged with the treatment system. While it should be noted that these results do not prove that treatment caused these changes in patient behaviour (or prevented relapse in the case of the 'continued low-level'

group), they shed light on the heterogenic development of OUD and pose further questions of the treatment system.

To varying extent, these three groups appear to no longer be in treatment. In the case of the 'continued low-level' group, it is appropriate to ask whether OST is suitable given their minimal use of illicit opioids throughout the five years in treatment. The 'rapid decreasing' group appears to have achieved abstinence by Year 2 and is maintained in treatment for another three years. The 'gradual decreasing' group achieve abstinence by Year 5.

At what point should clinical discussions move away from maintaining a patient on an opioid substitution treatment? This is a difficult question and will fall to the specific clinician, alongside their multidisciplinary group, and the specific patient to decide when this may be appropriate. Clinical guidelines in England point to the importance that the patient fully understands and is committed to the process of OST detoxification and is cognisant of the risks of relapse (Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group, 2017). When methadone dose is decreased, for example, it can induce craving and increase the risk of relapse (Greenwald, 2002). The risk of relapse is not simply about increased illicit heroin use. Alongside such an increase in use come the heightened risks of overdose, which can be fatal, and the potential to contract blood borne viruses. The detoxification process should therefore be slow, lasting up to around 12 weeks in an outpatient setting, and should be monitored closely. Signs that the detoxification is not going successfully, such as increased illicit heroin use, should result in the patient being offered a seamless reintegration into the OST or other treatment (Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group, 2017).

It has been argued addiction treatment should be conceptualised within a chronic disease management framework (McLellan et al., 2005). Treatments for asthma, diabetes or hypertension, for example, are not time-limited and continued engagement to monitor progress and alter treatment if appropriate is a positive patient-centred approach. While patients are engaged in treatment for OUD they are maintained within a protective environment. For example, for each year a patient is receiving OST their risk of mortality falls by 13% and this is despite the receipt of OST leading to a longer duration of drug use (Kimber et al., 2010). Being maintained in treatment is also associated with substantial reductions in offending behaviour (Ministry of Justice and Public Health England, 2017). It is also important to recall that Study 1 demonstrated that patients who had been engaged in treatment for two or more years had a much greater likelihood of successfully completing treatment. What is not presented from the studies in this thesis, but would be possible to elucidate with further research, is the extent to which other outcomes such as employment, housing and health have also changed when patients are maintained in treatment.

6.3 STRENGTHS OF THE STUDIES

The main strength across all three studies is the national, large scale and long-term follow-up of all individuals entering treatment for OUD. The utilisation of England's national administrative database to monitor relapse within six-months of discharge allowed for an objective summative measure of recovery to be used throughout these studies. Given the rate of short-term re-admission (even for those patients who have been discharged as having overcome their opioid dependence) incorporating this component into the outcome measure allows for a more accurate assessment of recovery. Conversely, it also enables the objective capture of whether or not, and how many times, a person has

previously engaged in treatment, which is an important negative predictor of treatment outcomes (Marsden et al., 2012b; Siguel and Spillane, 1978). Study 2 and Study 3 further refined the primary outcome measure by linking the records of those patients who had successfully completed treatment with the national register of fatal drug poisonings and the prison-based treatment system. This procedure guarded against the possibility that patients did not re-enter the treatment system simply because they were unable to do so. NDTMS, in this regard at least, has the advantage over other comprehensive administrative datasets (Alterman et al., 2001; Sahker et al., 2015; Stahler et al., 2016).

Study 2 and Study 3 made extensive use of the Treatment Outcomes Profile (Marsden et al., 2008) to measure change in heroin and concurrent substance use throughout patients' long-term enrolment in treatment. This 'concurrent recovery monitoring' (McLellan et al., 2005) provides a potent platform for policy makers and researchers to efficiently evaluate the effectiveness of community-based treatment under routine conditions. Previous research using the TOP has focused only on six-month outcomes (Marsden et al., 2012b, 2011, 2009), but these two studies demonstrated that deeper insights into the course of OUD can be gained through the appropriate application of modern sophisticated statistical methodologies.

6.4 LIMITATIONS OF THE STUDIES

Several limitations are need to be acknowledged. Study 1, in which a latent class analysis indicated four sub-types of heroin user, was based on the information submitted to NDTMS at the start of treatment in 2008/09. It is possible, as different drug use patterns come to the fore (such as the concurrent use of novel

psychoactive substances or gabapentinoids) that a different class structure could emerge if this approach was applied to individuals currently starting treatment.

NDTMS is a 'core dataset' of important variables used at many different levels, from treatment service managers to treatment purchasers to government officials. While all available covariates in NDTMS were screened for inclusion in the various models throughout Studies 1-3, other variables could further influence the likelihood of sustaining recovery, such as recovery strengths (Gossop et al., 2002d), treatment motivation (Simpson and Joe, 1993) and engagement (Simpson et al., 1995). It is also noteworthy that while certain adverse childhood experiences such as sexual exploitation, domestic abuse or intentional self-harm are recorded on NDTMS for those accessing young people's specialist addiction services, these items are not available within the adult core dataset. Capturing these experiences is important given their strong correlation with drug and alcohol dependence (Fuller-Thomson et al., 2016; Giordano et al., 2014) and, together, may represent an important confounding variable. One recent study, for example, estimated that almost 60% of heroin/crack prevalence could be attributed to adverse childhood experiences (Bellis et al., 2014), and childhood trauma is associated with prolonged use of benzodiazepines, which in turn are a risk factor for fatal and non-fatal overdose (Darke et al., 1996; Olfson et al., 2018; Vogel et al., 2011).

Capturing multimorbidity on NDTMS has also been a long-standing issue. The item 'dual diagnosis', which is defined as the presence of a diagnosed mental health disorder alongside the patient's substance use disorder has traditionally been poorly completed and could not be utilised in any other national cohort study (Eastwood et al., 2018a; Marsden et al., 2012b, 2011, 2009; Peacock et

al., 2018; Willey et al., 2016b). It has recently been replaced with a self-reported 'mental health treatment need' item and it has yet to be seen if this will be completed with greater rigour.

It is also important to note that while Study 1 reported that 13% of patients presented to treatment reporting an adjunctive alcohol addiction problems and Study 3 revealed that around 40% of patients reported alcohol consumption on each of the 11 assessment points, NDTMS does not capture any metric pertaining to alcohol-related impairment. This is important as it has been estimated that 50-80% of individuals with alcohol use disorder will experience mild to severe neurocognitive impairment and such impairment might limit the likelihood of positive treatment outcomes (Bates et al., 2002).

Also applicable to each of the studies is the possibility that patients underwent other forms of interventions that could have had an impact on the primary outcome measure, such as attending Alcoholics Anonymous or privately-funded residential treatment. These are not, however, captured by NDTMS and so it is not possible to assess the potential impact. Nonetheless, it is important to recognise that the E-value parameter estimated in Study 2 suggested that such variables would need to have an adjusted odds ratio of almost three to mitigate the association between trajectory membership and outcome.

Of particular relevance to Study 2 and Study 3 is that NDTMS does not actually capture the quantity of heroin and other drugs being used, only the frequency of use. It is possible that analysis of composite frequency by quantity metrics would yield different substance use trajectories. Further, it may be that the 'continued

high-level' groups do in fact demonstrate improvements in terms of the quantity being consumed.

6.5 REFLECTIONS ON LATENT CLASS CATEGORISATION

In the three studies presented in this thesis, I have relied on a combination of variable-centred and person-centred approaches to evaluate treatment effectiveness for OUD. The person-centred approaches were Latent Class Analysis (LCA) and Latent Class Growth Analysis (LCGA), both of which fall under the rubric of structural equation modelling. I used LCA to estimate sub-populations of OUD patients based on the concurrent substance use disorders (SUD) with which they presented to treatment. Two-thirds (67%) of patients had at least one concurrent SUD at treatment admission and LCA was applied to identify four hidden sub-populations that described the associations among crack cocaine, cannabis, alcohol, other illicit opioids, benzodiazepines and other stimulants. LCGA, on the other hand, was applied to the repeated measures of heroin and other drug use over time to reveal distinct groups based on common trajectories of change. As statistical tools, LCA and LCGA reduced the complexity of the potential combinations of either concurrent SUD (LCA) or change over time (LCGA) and demonstrated that some sub-populations have a differential likelihood of achieving successful completion of treatment.

The Guidelines for Reporting on Latent Trajectory Studies (GRoLTS; van de Schoot et al., 2017) are relevant here. Within these guidelines are 21 areas recommended for inclusion in studies seeking to identify trajectory groups from longitudinal data. I have self-assessed my first LCGA study, Study 2, and believe it scored at least 13 out of the maximum of 21. Of the 38 studies reviewed by van de Schoot et al (2017), only 2 studies scored at this level or above, indicating that

Study 2 was relatively well described. A well-described study does not, however, mitigate the risk of reification as outlined by Sher et al (2011). In brief, Sher and colleagues identified that many studies assessing latent trajectories within the alcohol field tended to report four recurring types including a consistently “low” group, an “increase” group, a “decrease group” and a consistently “high” group. These typologies emerged with sufficient regularity as to raise suspicions on the method. These are effectively the heroin trajectory groups identified in Study 2 except there were two ‘decrease’ groups and the ‘increase’ group had initially shown some reduction in heroin use frequency. Sher et al acknowledged that the ‘statistical abstractions’ that generate trajectory groups may be useful under some circumstances but there is a risk that they do not, in themselves, reveal fundamental developmental trajectories.

On reflection, the utility of the approach may lie not in the patterns of change that are revealed per se, but in the kind of clinical questions that can be asked of the addiction treatment field as a result of identifying these patterns. Some patients are less responsive to change and Study 3 demonstrated that heroin unresponsiveness overlapped with crack cocaine unresponsiveness. Highlighting the long-term need for treatment strategies that include a focus on concurrent crack cocaine use is clinically appropriate. It is also clinically appropriate to ensure that all patients accessing treatment for OUD are in receipt of a dose known to be effective in suppressing illicit heroin use.

6.6 LIMITATIONS OF NDTMS

Throughout the process of designing, conducting and publishing the three studies presented in this thesis, several problematic areas pertaining to NDTMS came to light that could potentially have impacted on successful publication:

- (1) diagnostic information;
- (2) identifiers;
- (3) gaming the system;
- (4) benzodiazepines;
- (5) national scope.

6.6.1 DIAGNOSTIC INFORMATION

When patients are registered on NDTMS, they are asked to name up to three 'problematic substances' that they are seeking treatment for. At no point does NDTMS capture whether or not these individuals are presenting with dependence on a particular substance or the severity of that dependence (although it should be noted that the Severity of Alcohol Dependence Questionnaire (SADQ; Stockwell et al (1983, 1979) was incorporated in April 2017). This point was picked up in the peer review process during the submission of the paper reporting Study 2, namely how are OUD diagnoses obtained and standardised across local treatment systems? I argued that such diagnoses are obtained during the initial triage assessment and subsequent full clinical assessments, which sit outside the core dataset NDTMS, and can include the Structured Clinical Interview for DSM or based on ICD-10 criteria. While this was accepted by *Drug and Alcohol Dependence*, it is clearly a weakness in a national administrative dataset designed to monitor the effectiveness of specialist drug and alcohol treatment. Using DSM nomenclature, is the dependence mild, moderate or severe? In ICD-10 terminology, is the patient being treatment for harmful use or dependence?

There are two immediate issues arising from the diagnostic information not being centrally collected. These relate to the status of patients at the start of treatment and at the end of treatment. At the end of treatment, the use of a severity of

dependence tool would enhance the ability of NDTMS to verify, at least internally, that the 'successful completion' accurately reflects remission from OUD. As it stands, it is assumed that this discharge code denotes that a patient is in remission from OUD, is abstinent from all opioids and crack cocaine, has completed all opioid pharmacotherapy and psychosocial interventions, has met all care plan goals and there is a mutual agreement to exit treatment. Such assumptions are, at best, questionable. The DSM approach would allow for an assessment of 'early' or 'stable' remission, while the ICD approach would at least be able to indicate the absence of harmful use or dependence. That said, incorporation of either a DSM or ICD assessment at the point a patient is exiting the treatment system would only demonstrate that NDTMS reporting is internally consistent and would not necessarily confirm that dependence has been overcome (see Section 6.6.3). It would be prudent for national administrators to validate the reporting accuracy of this discharge code by, for example, drawing a random sample of patients successfully completing treatment for urine screening.

For patients entering the treatment system, on the other hand, the routine availability and reporting of severity of dependence could inform the treatment plan and early discussions with patients as to what level of methadone, for example, they might be titrated on to. More importantly, however, Study 2 highlighted that around 15% of patients admitted to treatment for OUD reported using no illicit opioids in the 28-day period immediately prior to admission. This was also raised by the peer review process and I argued successfully that many national studies of OUD patients report varying proportions of patients who do not use illicit opioids prior to admission. Reasons for this may vary. It is reasonable to presume that one reason was to manage patients entering community-based treatment following release from prison. Another might be that a pregnant patient

felt she might restart using illicit opioids without a small dose of methadone. Neither of these account, however, for the entire 15%. It is important to remember that these individuals were all receiving OST and there are safeguarding issues that cannot be ignored. The routine use of a severity of dependence tool alongside the Treatment Outcomes Profile could potentially highlight instances where OST is not appropriate. It could also serve as an important covariate in models assessing treatment effectiveness.

6.6.2 IDENTIFIERS

There is one important issue which has received little attention. An individual patient in NDTMS is effectively a construct. An 'individual' is created from the set of first name initial, surname initial, gender, date of birth and, crucially, local authority of residence. This particular situation is a throwback to the early development of treatment databases in the 1980s (Strang et al., 1991). It was considered important at the time, in order to increase compliance with reporting to the database, that patient anonymity was preserved and the system evolved only accepting limited identifiers to ensure individuals were not double counted. Should any of these identifiers change, however, a new individual is constructed on the system.

As mentioned in the preceding section, there is a sizeable minority of individuals who appear to be initiating OST even though they have reported no heroin use in the period immediately prior to admission. It is possible, indeed likely, that many of these were not actually new to treatment but instead it was a result of the way in which NDTMS constructs individuals. Where individuals start and finish treatment at the same treatment provider, there is no problem. It is a problem, however, where individuals switch the local authority in which they live frequently,

such as in London where the boundaries are much closer together than, say, the northern parts of England. As the local authority of residence is changed, a new individual is constructed within NDTMS. Other difficulties arise where patients change their names after getting married (or divorced), or a date of birth is corrected, or a transgender change is recorded on NDTMS or name variations (e.g. Tony and Anthony) are used at different treatment services. The records received centrally lack the person-specific information required to remedy this.

What would remedy this would be the inclusion of an administrative identifier that is truly unique to the individual, most obviously the person's National Health Service Number. Such inclusion has the potential, when embedded, to make tracking people across NDMTS easier and more accurate, and it would also enable seamless linkage with other large-scale databases such as the Hospital Episode Statistics. Other systems, such as the Scottish Drug Misuse Database contain a Community Health Index that allows for trusted linkage between, for example, methadone prescriptions and drug-related deaths (Gao et al., 2016). The Scottish model does not have an integrated data warehouse per se, but the data controllers for each of the datasets – including maternity, GP consultations, hospital admissions, clinical imaging, substance misuse, cancer registrations and so on – actively assess any given research proposal and provide a de-identified dataset to approved researchers when there are clear public benefits of doing so (Pavis and Morris, 2015). Incorporation of such an identifier is therefore technically possible. It only requires the strategic directive to do so, thereby ensuring appropriate information governance and oversight procedures are in place to protect the rights of patients reporting to multiple systems.

6.6.3 GAMING THE SYSTEM

Gaming is a term that refers to the misreporting of administrative data to achieve a desired aim and is not unheard of in substance misuse treatment. Introducing outcome-based contracting arrangements such as performance-based contracting (PBC) or payment-by-results (PbR), for example, may provide a perverse incentive to engage in such a practice. After the introduction of PBC in Maine, for example, it was shown that clinicians had a tendency to increase the reported level of alcohol use at the start of treatment and decrease the reported level of alcohol use at discharge, thereby boosting the apparent effectiveness of the treatment intervention (Lu and Ma, 2006).

In England, a PbR programme was piloted in eight local authorities between 2012 and 2014. Recent analysis of that programme demonstrated that in-treatment outcomes such as abstinence from illicit drug and alcohol improved markedly, as too did injecting behaviour (Jones et al., 2018). These are precisely the kinds of outcomes that could be easily gamed should there be a desire and an incentive to do so. In contrast, however, the evaluation incorporated an objective outcome similar to that used in the three studies presented in this thesis (i.e. successful completion and non-re-presentation over 12-months) and showed that pilot areas actually deteriorated relative to non-pilot areas. These contradictory findings are difficult to reconcile, but a cynical reading might suggest the subjective in-treatment benefits (i.e. gains in self-reported alcohol and drug use and injecting behaviour) may have been inflated.

Treatment commissioners partly rely on statistics generated from NDTMS during their evaluation of contract bids. Falsifying reports to NDTMS is tantamount to fraud. That said, it is still possible for misguided services to 'game' their reporting

to NDTMS. An anonymous clinician, writing in *The Guardian* newspaper, highlighted one such area. As aggregated data on patients dropping out of treatment are reported back to managers and commissioners of services (and this counts negatively towards the provider), the clinician reported that one way to limit the damage is to simply “...not start the most chaotic people in treatment in the first place. People aren’t refused treatment but they are asked to jump through hoops before structured treatment is commenced” (*The Guardian*, 2017).

While not readily testable in NDTMS, perhaps – if these pre-treatment ‘hoops’ were systemic – this is one of the reasons why the number of patients accessing treatment for OUD is in decline and why waiting times to access treatment in England appear to be extremely good. Individuals presented to treatment with opiate addiction problems have an average waiting time of 1.7 days to start treatment and 98% commence treatment within three weeks (Public Health England, 2018a). It would seem reasonable to conclude that rapid access to treatment is readily available, but is this an accurate assessment?

It is important that national administrators of NDTMS invest in auditing local services. A greater understanding of local processes and policies may provide insight into the reason(s) for falling numbers of OUD patients accessing treatment, such as the pre-treatment ‘hoops’ mentioned above. For other in-treatment outcomes, such as heroin abstinence, a risk-adjustment model would highlight which services or local authorities are performing above or below the expected level for their given caseloads and would provide fertile ground for conducting audits. In terms of waiting times, it should be possible to draw a random sample of treatment services with particularly low waiting times and interview recent admissions to those services to gain a greater understanding of

what a 'wait' means to patients accessing the system and whether or not this is represented by NDTMS figures.

6.6.4 BENZODIAZEPINES

While the misuse of benzodiazepines can be recorded at the start of treatment as one of the three substances a patient declares as problematic and in need of treatment (see Section 6.6.1), it is unfortunate that the illicit use of this class of drug is not routinely collected during a patient's time in treatment. The reason it is not included on the Treatment Outcomes Profile is that the test-retest reliability was shown to be poor in the psychometric evaluation of the tool (Marsden et al., 2008). Specifically, while the test-retest of benzodiazepine prevalence was satisfactory ($\kappa \geq 0.61$), the inter-rater intraclass coefficient did not reach the specified threshold for 'excellent' ($\text{ICC} \geq 0.75$). Similar findings were reported in Chile (Castillo-Carniglia et al., 2015) and Australia (Ryan et al., 2014b). The Chilean Government, however, decided the clinical importance of including illicit benzodiazepines over-ruled the statistical criteria, while Australia reintroduced the item and included both prescribed and illicit benzodiazepines. In the latter example, this was due apparently to the difficulty in differentiating between the misuse of prescribed benzodiazepines and those illicitly obtained and was in the context of high prevalence of benzodiazepine use in the country.

In response to a query by the peer reviewers of Study 3, concerning the meaning of the 'unspecified drug' utilised in the study, it was argued successfully that this substance was likely to be illicit benzodiazepines because in England illicit benzodiazepine use affected 10% of all patients in treatment for OUD in 2017/18 (Public Health England, 2018a). This is a substantially higher proportion than other substances that might be recorded under the 'unspecified substance' on

the TOP such as anti-depressants, hallucinogens, volatile solvents, or major tranquillisers (each <1%).

The use of benzodiazepines alongside heroin appears to play a central role in both fatal and non-fatal overdose (Cousins et al., 2011; Darke et al., 1996; Darke and Zador, 1996; Farrell and Marsden, 2008; Olfson et al., 2018; Yamamoto et al., 2019). The concurrent use of benzodiazepines can affect the metabolism of methadone and is also associated with deteriorated hepatic function in those with HCV (Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group, 2017). It is critical, in light of these risks – particularly at a time of increasing drug-related deaths in Great Britain (National Records of Scotland, 2019; Office for National Statistics, 2019) – that drug workers, commissioners and national administrators to have accurate information on the use of illicit benzodiazepines. It would seem prudent for this class of drug to be incorporated into the standard TOP assessment.

6.6.5 NATIONAL SCOPE

NDTMS collates information on all individuals accessing publically funded specialist alcohol and drug addiction treatment services. At least, it is intended to. The number of individuals accessing treatment for OUD has been falling in recent years, at a time when the estimates of the OUD population has remained fairly stable (Hay et al., 2019; Public Health England, 2018a). While it is possible that the reduction in number is solely the result of an overall reduction in funding for treatment services (Drummond, 2017; Kalk et al., 2018) or that patients are declining treatment when faced with pre-treatment hurdles, it is also possible that individuals are accessing help from outside the current national treatment system. Privately-funded residential treatment facilities, for example, are

available for those who can afford them. Given the cost of such facilities, it is unlikely to account for a large number of patients with OUD. Of more practical concern is the potential for GP services, commissioned outside the local authority remit for drug and alcohol treatment, to treat patients with OUD. The concern lies not so much in whether or not patients are receiving adequate medication to help overcome their illicit use of heroin, but whether all other ancillary interventions are being made available, such as psychosocial interventions.

In my position at PHE I have the opportunity to interview commissioners about the NDTMS data collected in their area. In one such recent meeting (March 2019), I was informed of one particular GP practice that may be seeing up to 200 OUD patients and that these are not reported to NDTMS. It is difficult for national administrators to know how widespread such an issue may be, or how they can encourage NDTMS reporting in the absence of any financial incentive to do so.

It is possible, however, to examine GP prescribing data in England as these are regularly published by NHS Digital. Using the December 2018 data, for example, one can see that 139 GP practices in England (1.5% of the 9,473 reporting in that month) issued more than 100 prescriptions for methadone and the mean amount issued per prescription was more than 600mg (NHS Digital, 2019). It is of course feasible that some of these practices were issuing methadone for chronic pain management purposes, but it is likely that many were issued for treating OUD. In total, these 139 practices issued 96,596 prescriptions for a total of 58,219,599mg methadone in December 2018. If one assumes the intention was to provide 60mg or 120mg per person per day, then it is possible that 15650-31,300 individuals were being treated for OUD by General Practitioners. After removing practices that are clearly operating in conjunction with specialist addiction services (i.e.

‘shared care’), there remained 29 practices that may be operating outside of NDTMS reporting. These 29 practices issued 2,788 prescriptions for a total of 1,805,071mg methadone, suggesting that 485-970 patients in December 2018 were being treated for OUD outside the national reporting system. A more detailed examination of these data is required and such practices should be encouraged to submit to NDTMS.

6.7 FUTURE RESEARCH

The cohort of heroin addicts who have been in opioid substitution treatment continuously over a five-year period present a unique and valuable opportunity for future research. While some effort was made to examine the relationship between longitudinal heroin use and the use of alcohol and other drugs, a number of important research questions remain.

Evidence suggests that unemployment, homelessness, poor physical and psychological health and drug use are mutually reinforcing in their damaging effect. In a recent review of unemployment and substance use, Henkel (2011) noted that unemployment is a risk factor in the development of a substance use disorder and that drug use increases the likelihood of unemployment and decreases the likelihood of finding or keeping a job. Worklessness has also been related to health inequalities (Bambra & Popham, 2010; Bambra, 2011) and early unemployment has been shown to contribute to later adult health problems (Hammarstrom and Janlert, 2002). Transitioning away from paid employment can have a deleterious effect on psychological well-being while gaining a job has been shown to reduce psychological distress (Thomas et al., 2005). Being employed is associated with a decreased mortality risk in a population of HIV-positive drug users (Richardson et al., 2014).

Taken together, the complex interweaving of personal, social and economic problems over the life-course may contribute to the chronic course of OUD (Eastwood et al., 2018b; Grella and Lovinger, 2011; Hser et al., 2007). One potential way to disentangle these relationships is through the use of cross-lagged panel models. These models are relevant when estimating the relationship between two or more co-occurring phenomena that are repeatedly measured over time. They are particularly useful in establishing the direction of association (Selig and Little, 2012). More specifically, the cross-lagged panel model enables the researcher to simultaneously assess the stability of a given phenomenon while also estimating the time-ordered effect of each phenomena on the others, controlling for prior levels (Kim et al., 2018).

In the context of the cohort of heroin addicts continuously enrolled in OST over a five-year period, the repeated assessment of patients using the Treatment Outcomes Profile is suited to this approach. Within a structural equation modelling framework, a latent 'drug use' variable at each time point can be measured based on the responses given to the seven available substance use items. Similarly, a latent 'recovery capital' variable can represent the responses to employment and housing problems at each assessment and a latent 'health' variable can represent the physical health, psychological health and quality of life items. These three latent variables can then be used for the cross-lagged modelling and enabled the exploration of

(1) whether or not higher levels of drug use leads to deteriorating recovery capital and health;

(2) whether or not poorer recovery capital leads to worsening drug use and health;

(3) whether or not higher levels of health leads to improvements in drug use and recovery capital;

(4) whether or not bidirectional effects exist between two or more of these variables.

6.8 FINAL CONCLUSIONS

The studies presented in this thesis investigated the long-term treatment response in a national cohort of heroin addicts in England. Sub-populations were identified cross-sectionally at treatment admission based on concurrent substance use disorders and longitudinally based on the pattern of substance-specific responses over five years of treatment. Study 1 demonstrated that spending at least two-years in treatment substantially increased the likelihood of recovering from heroin addiction problems. Study 2 demonstrated that, for some, achieving abstinence can take several years and that individuals on trajectories tending towards abstinence eventually overcome their addiction. Study 3 demonstrated that those heroin addicts who make the least improvement in terms of continued heroin use are also those individuals for whom crack cocaine poses a continued challenge. Taken together, these studies highlight the importance of appropriate application of sophisticated statistical techniques in discerning obstacles faced by the treatment system and the opportunity this represents to identify potential solutions to overcoming those barriers. Although not without its limitations, NDTMS is an important resource for all stakeholders involved in the treatment of addiction.

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APPENDIX A PUBLICATIONS



Full length article

Effectiveness of treatment for opioid use disorder: A national, five-year, prospective, observational study in England

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ABSTRACT

Background: This the first 5-year effectiveness study of publicly funded treatment for opioid use disorder (OUD) in England.**Methods:** All adults initiating treatment in 2008/09 in all 149 local treatment systems reporting to the National Drug Treatment Monitoring System ($n = 54,347$). Admission polydrug use sub-populations were identified by Latent Class Analysis. The treatment outcome measure was 'successful completion and no re-presentation within six months' (SCNR) analysed by multilevel, multivariable logistic regression and funnel plots to contrast outcome by treatment system.**Results:** SCNR was achieved by 21.9%. Heroin and crack cocaine users were significantly less likely to achieve this outcome than patients who used heroin only (adjusted odds ratio [AOR] 0.90; 95% confidence interval [CI] 0.85–0.95). Older patients (AOR 1.09; CI 1.07–1.11), those employed (AOR 1.27; CI 1.18–1.37) and those enrolled for longer treatment were more likely to achieve the outcome measure. After risk adjustment, the local treatment systems that achieved substantially better outcome performance (14/149) had a lower rate of opiate prevalence in the local population at time of study initiation (incidence rate difference [IRD] 4.1; CI 4.0–4.2), fewer criminal offences per thousand (IRD 28.5; CI 28.1–28.8) and lower drug-related deaths per million (IRD 5.9; CI 5.9–5.9).**Conclusions:** In an English national study, one fifth of patients successful completed treatment for OUD and did not present for further treatment within six months. Longer time in treatment increases the probability of achieving and maintaining clinical benefit from treatment. After risk-adjustment, an important minority of treatment systems achieve substantially better outcome performance.

1. Introduction

Heroin and non-medical opioids are associated with a substantial global burden of disease (Degenhardt et al., 2013). In the United States (US), it is estimated that 2.6 people per 1000 aged 12 and above used heroin in the past year (Jones et al., 2015). In Europe, the estimated annual heroin use prevalence is 4 per 1000 aged 15–64 (EMCDDA, 2015) and 7.3 per 1000 among people aged 16–64 in England (Hay et al., 2014).

Opioid use disorder (OUD), and the conceptually identical 'opioid dependence', is a debilitating and often chronic bio-behavioural disorder (DSM-5; American Psychiatric Association, 2013; ICD-10; WHO, 2016). People with OUD typically use illicit heroin and/or non-medical opioid pharmaceutical products, developing physiologi-

cally dependence and strong motivational urges. Around one quarter of opioid users develop OUD (Gable, 1993; Anthony et al., 1994). Left untreated, OUD typically follows a chronic course causing substantial health, social and economic problems (Hser et al., 2001; Grella and Lovinger, 2011; Hser et al., 2015). In the classic Grella and Lovinger study, half of the sample died and a quarter did not experience any sustained improvement in their drug use (Grella and Lovinger, 2011).

The OUD population is far from homogenous. Several behaviours are associated with increasing severity of the disorder (Marsden et al., 2014) and treatment effectiveness may vary between sub-populations. For example, drop-out is more likely among patients with comorbid psychiatric conditions and more criminal justice involvement in the year before treatment, and less likely among those living with dependent children (Evans et al., 2009). Ethnic minority populations

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have been reported to have a lower rate of treatment episode completion (Mennis and Stahler, 2016). An important sub-population are polydrug users, typically involving concurrent use of one or more of the following: alcohol, cocaine powder, smokeable (*crack*) cocaine and benzodiazepines (Darke and Hall, 1995; Monga et al., 2007; Harrell et al., 2012; Kuramoto et al., 2011). Heroin smokers who use crack cocaine are substantially less likely to be infected with Hepatitis C virus than those who inject heroin (Harrell et al., 2012). Opioid-polydrug users have been observed to have greater health and social problems (Leri et al., 2003) and a relatively poorer response to OUD treatment (Williamson et al., 2006; Marsden et al., 2011, 2009).

The majority of countries with a high prevalence of OUD have an array of well-developed treatment services. The opioid medications methadone and buprenorphine are front-line, randomised-controlled trial supported pharmacotherapies (Mattick et al., 2014, 2009). Some OUD patients may receive psychosocial interventions without opioid psychotherapy. Interventions are typically provided by specialist community, primary care and hospital providers. Inpatient withdrawal management and drug-free residential rehabilitation services are also available. In addition to case management, national clinical guidelines recommend psychosocial interventions to address cognitive and behavioural symptoms of OUD (e.g., National Institute for Clinical Excellence, 2007).

Internationally, there have been several longitudinal cohort studies of the effectiveness of these interventions as delivered under routine conditions by public treatment systems (e.g., Simpson and Sells, 1990; Stewart et al., 2002; Darke et al., 2007; Marsden et al., 2009; White et al., 2015). Taken together, these studies conclude that treatment is associated with reduced opioid use, drug injecting, and offending behaviour, and improvements in health (including a substantially reduced risk of fatal overdose), social functioning and employment.

Longitudinal cohort studies are time consuming and expensive. Public accountability means that the commissioners of publicly funded services need information on the effectiveness of treatment as it is delivered. Various proxy measures of outcome have been used in treatment systems research, including unsanctioned discharge (drop-out) from treatment and retention (Brorson et al., 2013; Stark, 1992; Faggiano et al., 2003). A commonly used measure is the proportion of patients treated who complete treatment successfully (Alterman et al., 2001). This indicator is associated with reduced drug use (Evans et al., 2009; Kornør and Waal, 2005), increased employment (Lang and Belenko, 2000; Zarkin et al., 2002; Evans et al., 2009; Sung and Chu, 2011; The TOPPS-II Interstate Cooperative Study Group, 2003), lower arrests and incarceration (Campbell et al., 2007; Evans et al., 2009; Gifford et al., 2014; Finnigan, 1996), and a reduced likelihood of readmission to treatment services (Luchansky et al., 2000). In the US, substantial inter-state (Arndt et al., 2013) and regional variation in completion rates have been reported (Hawkins et al., 2014), and this is now monitored at the federal/government level (Stahler et al., 2016).

The 'successful completion' indicator has a key limitation – it does not capture the extent to which treatment benefit is enduring. This is important because relapse is common, affecting 50–60% of people within six months after leaving treatment (McLellan et al., 2005). The process of achieving stable recovery from OUD may involve several cycles of treatment over a decade or more (Dennis et al., 2005; Hser et al., 1997).

To fully assess the effectiveness of treatment systems, national administrative databases need to be able to capture this process, yet the requirements of such systems are difficult to implement. In the US, the absence of a patient consent prevents linkage across consecutive treatment episodes. At the national level, the impact of this is twofold: it is not possible to objectively assess whether an individual has previously engaged in treatment (an indicator of patient-level complexity (Marsden et al., 2012; Siguel and Spillane, 1978). It is also not possible to determine whether a patient's successful completion status is enduring.

England has a well-developed public treatment system for drug use disorders with service delivery involving specialist clinics in the National Health Service (NHS) and non-governmental sector. Services are commissioned by 149 local treatment systems across the country aligned to local government geographical boundaries. All public providers report clinical and effectiveness data to the National Drug Treatment Monitoring System (NDTMS). NDTMS is operated by Public Health England and provides outcome monitoring and performance benchmarking for each local system (see Marsden et al., 2009 for an operational description). The latest national report shows that 28% of people treated for OUD complete treatment successfully (Public Health England, 2016a).

With temporal linkage of episodes, NDTMS can record re-presentation to treatment as a proxy remission indicator. To our knowledge, a 'successful completion and no re-representation' outcome measure has not been used in previous OUD treatment systems research. Accordingly, the aim of this study was to estimate the effectiveness of OUD treatment in England for OUD using this indicator and contrast the effectiveness of local treatment systems.

2. Methods

2.1. Design

This was an English national, five-year, prospective, observational cohort study of publicly-funded, specialist treatment services for OUD reporting to the NDTMS, and reported following the STROBE guideline for observational research (Elm et al., 2007). The population for the study was all adults (≥ 18 years) diagnosed with OUD who presented for treatment in England between 1 April 2008 and 31 March 2009.

The study included all local treatment systems and all operational specialist community agencies in the NHS and third-sector providing pharmacotherapies, psychosocial interventions and adjunctive support services for OUD in community, inpatient (short-term medically supervised withdrawal), and residential (drug-free rehabilitation) settings.

2.2. NDTMS database

NDTMS captures a core dataset of all clients entering the treatment system, and is designed to record key information at each stage of the treatment process. An initial triage assessment is conducted by clinical staff at each treatment service during the first face-to-face meeting following referral to treatment which can, in the case of self-referrals for example, take place on the same day. Where a treatment need is clinically indicated, the substance(s) and patient demographics are recorded on NDTMS and an appointment for a treatment intervention is arranged. The mean waiting time to initiate this intervention is 2.2 days for OUD patients, and 98% start treatment within three weeks (Public Health England, 2016a). Each treatment intervention received is recorded on NDTMS (Section 2.2.1). Treatment is not time-limited: patients are maintained in treatment for as long as clinically indicated (Section 2.2.2).

2.2.1. OUD treatments

The opioid pharmacotherapies included methadone, buprenorphine and also naltrexone. Psychosocial interventions such as contingency management and motivational interviewing complement pharmacotherapy and target underlying psychological aspects of dependence. In addition to opioid pharmacotherapy and/or psychosocial interventions, a patient's treatment programme could include adjunctive 'recovery support' services, including: facilitated access to mutual aid; complementary therapies; and family, housing, employment, education and training supports.

2.2.2. Treatment episodes and journeys

Following the NDTMS reporting protocol, each patient-level ‘treatment journey’ comprised: a single episode of pharmacotherapy or psychosocial intervention provided by a clinic; enrolment in concurrently delivered medication and psychosocial interventions (from one or more clinics); or a continuing care package in which an intervention was followed by one or more further interventions. Episodes commencing after 21 days are classified as a new treatment journey (Public Health England, 2015). Recovery support services are offered concurrently or following a treatment episode. Patients are regularly reviewed, treatment provision changes, and at the end of the ‘treatment journey’, patients who overcome their dependence are successfully discharged from the treatment system.

When a patient was discharged from treatment, one of the following exit reasons was recorded: successful completion; drop-out (patient left treatment without discussion or before completing their care plan); unsuccessful transfer (patient was referred to another treatment service but does not enter treatment within 21 days); incarceration (treatment is prematurely terminated due to criminal justice action); or patient died. After this point, further treatment was classified as a new treatment journey.

2.3. Outcome measure

The outcome measure for the study combined two components: successful completion and no re-presentation. Successful completion was assigned to each patient that was reported by the clinic as meeting the following criteria within five years (ending 31 March 2014):

- in remission from OUD;
- abstinent from all opioids and crack cocaine;
- completed all opioid pharmacotherapy and psychosocial interventions;
- met all care plan goals, with mutual agreement to exit treatment.

For the ‘no re-presentation’ element of the outcome measure, we judged that a six-month period was reasonable (ending 30 September 2014). Therefore, the effectiveness measure was assigned to those patients who met the above criteria at exit from treatment and did not re-present for any treatment within six months (‘successful completion, no re-representation’, SCNR for economy herein).

2.4. Covariates

We followed an integrated variable-centred and person-centred approach to evaluate treatment effectiveness for OUD using the following patient demographic, clinical information and previous treatment exposure (all recorded at initial assessment):

2.4.1. Demographic

Sex; age (centred at 18 years and grouped in five-year increments); Black and Minority Ethnicities (BME: a legal monitoring requirement (*Race Relations (Amendment) Act*, 2000)); employed; housing problems (defined primarily as having no fixed abode, but can also include squatting, short-term hostel/Bed and Breakfast, staying with friends/relatives; [(homeless, herein)]).

2.4.2. Social deprivation

Local area deprivation was measured by the Indices of Multiple Deprivation (IMD; (Department for Communities and Local Government, 2007)). IMD data were linked to NDTMS based on the patient’s residential postcode district or the location of their first treatment provider in instances of missing postcode information.

2.4.3. Injecting status

Three levels of injecting status are recorded at the start of treatment:

never injected; lifetime history of injecting, and current injector

2.4.4. Career length

The number of years between first initiating opioid use and enrolment in the index treatment journey (length of the substance-using career). This measure was mean centred and coded in five-year increments.

2.4.5. Treatment history

Referral route into treatment was categorised into whether the patient was self-referred, referred via the criminal-justice system or other (e.g., referral from health service or substance abuse service). Whether an individual had previously accessed treatment was also included.

2.5. Statistical analysis

All analyses were done in Mplus (version 7.11) and Stata (version 13.1).

2.5.1. Drug use sub-populations

Given anticipated heterogeneity in drug use profile of the OUD population at presentation to treatment (Monga et al., 2007; Public Health England, 2016a), we used latent class analysis (LCA) in Mplus to identify discrete sub-populations of OUD patients who presented for treatment with concurrent disorder with one or more of the following 6 substances: crack cocaine; cannabis; alcohol; non-medical opioids; stimulants (powder cocaine and *d*-amphetamine) and benzodiazepines.

The LCA was iterative with an unconditional 1-class model initially fit to the data and sequentially increased to a 6-class model. Each model used 5000 random sets of starting values to guard against convergence on local maxima (McLachlan and Peel, 2000) and a minimum class size of 5% of the cohort was set for utility (Willey et al., 2016; Borders and Booth, 2012). Class identification was informed by posterior fit statistics, including the Bayesian and Akaike information criteria and entropy. A multinomial logistic regression was then used to characterise the latent classes on the patient-level characteristics. Given the hierarchical structure of the study, with patients clustered in treatment services and services clustered in local treatment systems, confidence intervals (CI) were calculated using robust standard errors.

2.5.2. Outcome analysis

A three-level, multivariable logistic regression was used for the analysis of the outcome measure (Stata command: *meqrlogit*). The complete-case model contained the following random intercepts: patients (level one); treatment services (level two); and local treatment system (level three). Model discrimination and variation (at level two and three) was estimated by c-index (Hanley and McNeil, 1982), and intra-cluster correlation (ICC), respectively.

Reflecting the hierarchical design of the study (Hofmann, 1997; Heo and Leon, 2008) and with alpha, statistical power and a medium effect size on the outcome measure pre-set (0.05, 0.90 and $f^2 = 0.15$, respectively (Cohen, 1988)), we ensured that there were at least 15 cases per covariate in the regression analysis to minimise overfitting (Green, 1991; Babyak, 2004).

With no contrary evidence that data loss was missing-at-random (Little and Little, 2002), a multiply imputed dataset was computed by chained equations (Stata command: *mi: impute chained*). An all-case multivariate logistic model was run to check on potential bias and loss of precision (Sterne et al., 2009). To achieve a relative efficiency above 98% (Rubin, 1987), and to ensure that reduction in power was less than 1% (Graham et al., 2007), 20 datasets of probabilistic values were created, each analysed separately, and then combined using Rubin’s rules.

2.5.3. Analysis of local treatment systems

A fixed-effects approach was used to determine the relative effectiveness of each local treatment system because random intercepts could mask real variation in achieving the outcome (Marsden et al., 2012). For each treatment system, predicted outcome probabilities were summed across patients and divided by the number of patients treated in the area. A risk-adjusted outcome rate was then calculated by dividing the expected rate by the observed rate and multiplying this by the national average.

A funnel plot with 95% control limits (Spiegelhalter, 2005) then identified areas where outcome performance was better or worse than expected (where the area was located above or the control limit, respectively). Local treatment systems rates of opiate prevalence, offending and drug-related deaths were contrasted by incidence-rate ratio.

Outcome performance was contrasted using pooled estimates of the rate of opiate users per thousand inhabitants (Hay et al., 2010), incidence of drug related deaths per million inhabitants (Public Health England, 2016b) and the criminal offence rate per thousand inhabitants (Office for National Statistics, 2016). The offending rate was based on the local area population estimates used in the development of the opiate prevalence estimates (Hay et al., 2010).

3. Results

3.1. Study cohort and follow-up

The population for the study was all adults (≥ 18 years) diagnosed with OUD who presented for treatment in England between 1 April 2008 and 31 March 2009 ($N = 56,156$). As 1799 (3.2%) people did not commence treatment by 31 March 2014, they were removed from further analyses.

Patients in the cohort ($n = 54,357$) commenced treatment for OUD in 1421 specialist clinics and primary care teams in the National Health Service (NHS) and the non-governmental sector (median of 12 patients per service; IQR 3–45), and in all 149 local treatment systems in England (median 302 patients per area; interquartile range [IQR] 184–470)].

At the end of the five-year period, 7890 people (14.5%) were continuously enrolled in treatment for OUD. Given the aims of the present study, this group was removed. Among the final all-case cohort ($n = 46,467$), 9007 patients (19.4%) had missing observations on one or more covariates, yielding a complete-case cohort of 37,460. The covariate with the highest level of missing data was length of heroin use career (11.4%), followed by employment status (9.1%), housing status (3.4%) and injecting (3.4%).

3.2. Drug use sub-populations

At clinical assessment, 67% of patients had a concurrent substance use disorder, as follows: crack cocaine (44.1%), cannabis (14.1%), alcohol (13.3%), other illicit opioids (11.4%), benzodiazepines (9.4%) and other stimulants (8.8%).

Table 1 displays the results of the LCA models. The value of each information criterion (Akaike, Bayesian and adjusted Bayesian) reduced as the number of classes increased, indicating successively better fitting models. The bootstrapped likelihood ratio test confirmed that each model was a statistically better fit than the preceding one. Entropy was high (> 0.8) for all except the 3-class solution, which reflected relative uncertainty in the assignment of individuals to the third class. The 5-class and 6-class solutions resulted, however, in at least one class with less 5% of the cohort. Accordingly, we judged that a 4-class solution best identified the heroin and other drug use sub-populations at treatment admission, and labelled these as follows:

- **Class 1** ($n = 30,339$, 56%: *heroin low level concurrent drug use*

disorders);

- **Class 2** ($n = 2794$, 5%: *heroin, crack, alcohol*);
- **Class 3** ($n = 17,907$, 33%: *heroin, crack*);
- **Class 4** ($n = 3257$, 6%: *heroin, crack, cannabis*).

3.3. Characteristics of the cohort

Table 2 shows the demographic and clinical characteristics of the cohort and the results of the multinomial logistic regression analysis of the profile of the drug problem classes on socio-demographic, injecting, heroin career and treatment referral characteristics (with the heroin and low concurrent drug use disorders [class 1] as the referent).

There were relatively less employment and more homelessness among the members of classes 2, 3 and 4. Class 4 was also relatively more likely to be referred to treatment from the criminal justice system (35.3%) and have previous OUD treatment (50.4%).

3.4. Treatment exposure and status at exit

Patients in the cohort received a median of 31.0 weeks of treatment (IQR 12.6–80.3) and 13,360 (28.8%) successfully completed their treatment journey (Table 3). One-third (32.1%) of discharged patients were readmitted for further treatment for substance use disorders within six months.

Readmission was more likely for those who were incarcerated (re-admission rate 45.2%; odds ratio [OR] 2.67; 95% CI 2.50–2.82), dropped out (re-admission rate 34.8%; OR 1.72; 95% CI 1.63–1.81), or transferred unsuccessfully to another SUD treatment service (re-admission rate 28.3%; OR 1.27; 95% CI 1.20–1.35) compared with those who completed treatment successfully (re-admission rate 23.7%).

Relative to Class 1, patients assigned to Class 2 and Class 4 were less likely to have received opioid pharmacotherapy, Class 4 was more likely to have received psychosocial interventions, and Class 2 received more in-patient services. Class 1 received the least amount of residential services and was retained in treatment longer than any other class. Class 3 reported more incarceration, unsuccessful transfers and drop-outs, but less deaths, while Class 2 had fewer incarcerations but more drop outs. There were relatively fewer deaths in Class 4.

3.5. Successful completion of treatment and no re-presentation within six months

Overall, 21.9% of the cohort (10,194) attained the SCNR outcome (Table 3). Class 3 were less likely to achieve the outcome. After negative multi-collinearity screening for all covariates, the results of the unadjusted, covariate adjusted complete-case ($n = 37,460$) and multiply-imputed, all-case ($n = 46,467$) analyses are shown in Table 4.

The complete- and all-case models yielded very similar covariate estimates. In the all-case model, with statistically significant adjustment for clustering effects associated with treatment agency and local treatment system (ICC 0.13 and 0.17, respectively) there was satisfactory discrimination between patients who achieved the SCNR outcome (c -index 0.74; 95% CI 0.74–0.75).

There was an increased likelihood of positive outcome among older patients, those with pre-treatment employment, and those who with longer time enrolled in treatment (particularly for more than 2 years; adjusted odds ratio [AOR] 2.60; 95% CI 2.43–2.78).

A negative outcome was associated with men, patients who were homeless before admission and in areas of greater social deprivation (gradient with likelihood lowest at highest quintile; AOR 0.77; 95% CI 0.70–0.85); drug injectors; those referred from the criminal justice system; those with previous treatment for OUD; those with shorter heroin using career; and members of class 3.

Table 1
Unconditional latent class analysis of drug use at presentation to treatment (n = 54,347).

Parameter	Class 1	Class 2	Model ^a Class 3	Class 4	Class 5	Class 6
No. of parameters	6	13	20	27	34	41
AIC	266,371.29	264,740.91	262,525.26	261,201.63	260,527.17	260,033.40
BIC	266,424.71	264,856.65	262,703.32	261,442.02	260,829.88	260,398.43
aBIC	266,405.65	264,815.33	262,639.76	261,356.22	260,721.83	260,268.13
aBIC change (%)	–	–0.60	–0.82	–0.49	–0.24	–0.17
Entropy	–	0.999	0.718	0.830	0.861	0.857
BLRT	–	–133,179.65	–132,357.45	–131,242.63	–130,573.82	–130,229.58
BLRT reduction (%)	–	–	0.62	0.84	0.51	0.26
Class (probability)						
1	1.00 (1.00)	0.44 (1.00)	0.06 (0.99)	0.56 (0.83)	0.29 (0.99)	0.01 (0.71)
2	–	0.56 (1.00)	0.38 (1.00)	0.05 (0.99)	0.04 (0.97)	0.55 (0.79)
3	–	–	0.56 (0.69)	0.33 (0.99)	0.05 (0.99)	0.04 (0.99)
4	–	–	–	0.06 (0.99)	0.06 (0.99)	0.06 (0.99)
5	–	–	–	–	0.56 (0.84)	0.29 (0.99)
6	–	–	–	–	–	0.05 (0.98)

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; aBIC, sample-size adjusted BIC; BLRT, bootstrapped likelihood ratio test (all $P < 0.00005$).

Classification based on most likely latent class membership.

^a For the following drugs: crack cocaine, cannabis, alcohol, other opioids, benzodiazepines and other stimulants.

Table 2
Characteristics of the cohort and drug use sub-populations.

Covariate	Total n	(%)	Class 1 n = 30,339	Class 2 n = 2794	Class 3 n = 17,907	Class 4 n = 3257
<i>Socio-demographic</i>						
Male	41,099	(75.6)	(76.5)	(74.9)	(73.0)	(82.0)
Age ^a	32.9	(7.8)	32.9 (7.9)	34.2 (7.9)	33.0 (7.5)	31.9 (7.9)
Black/Minority Ethnic	7342	(13.5)	(10.9)	(15.8)	(15.9)	(22.4)
Employed	6222	(12.5)	(14.7)	(8.1)	(9.7)	(11.4)
Homeless	17,343	(32.9)	(29.5)	(43.1)	(36.8)	(35.1)
<i>Social deprivation:</i>						
Quintile 1 (lowest)	10,857	(20.0)	(21.6)	(19.9)	(17.1)	(20.4)
2	10,922	(20.1)	(19.9)	(21.9)	(20.1)	(20.3)
3	10,823	(19.9)	(19.9)	(23.3)	(19.3)	(20.2)
4	10,859	(20.0)	(19.8)	(18.9)	(20.3)	(20.6)
Quintile 5 (highest)	10,896	(20.0)	(18.7)	(16.0)	(23.2)	(18.5)
<i>Clinical</i>						
Heroin career ^a	11.4	(7.5)	(7.6)	(8.3)	(7.2)	(7.4)
<i>Drug injecting:</i>						
Never	17,715	(33.6)	(32.8)	(32.5)	(33.1)	(44.5)
Lifetime	18,004	(34.2)	(34.9)	(35.4)	(33.5)	(30.4)
Current	16,996	(32.2)	(32.3)	(32.1)	(33.4)	(25.0)
<i>Referral Source:</i>						
Other	17,453	(32.1)	(35.0)	(35.1)	(27.6)	(27.2)
Self	20,570	(37.8)	(39.4)	(37.6)	(35.2)	(37.5)
Criminal justice	16,334	(30.0)	(25.6)	(27.3)	(37.1)	(35.3)
Previous OUD treatment:	30,212	(55.6)	(55.6)	(52.4)	(57.0)	(50.4)
< 6 months	20,835	(38.3)	(35.3)	(45.1)	(41.4)	(44.1)
6 months to < 1 year	8917	(16.4)	(16.1)	(16.4)	(16.9)	(17.0)
1 year to < 2 years	8014	(14.7)	(15.4)	(14.3)	(13.6)	(14.9)
2 years to 5 years	16,591	(30.5)	(33.2)	(24.3)	(28.1)	(24.0)

Class 1: Heroin and low likelihood of problem substance use.

Class 2: Heroin, problem crack cocaine and alcohol use.

Class 3: Heroin and crack cocaine use.

Class 4: Heroin and crack and cannabis use.

Figures in parentheses in table are percentages unless otherwise stated.

Emboldened percentages and means are statistically significant ($P < 0.05$) from multivariable, multinomial logistic regression (Class 1: referent).

^a Year (SD).

3.6. Comparison of local treatment systems

Following risk-adjustment, 14 of 149 local treatment systems were classified as achieving performance that was better than expected on the SCNR outcome, and 38 local treatment systems achieved performance that was worse than expected (Fig. 1). In comparison to the

better performing areas, these 38 areas were characterised with a higher estimated level of opiate use in the local population (an extra 4.1 (95% CI 4.0–4.2) opiate users per thousand population), a higher level of drug-related offences (an extra 28.5 (95% CI 28.1–28.8) offences per thousand population), and more drug-related deaths (an extra 5.9 (95% CI 5.9–5.9) deaths per thousand population) (Table 5).

Table 3

Treatment interventions received, by treatment leavers, SCNR outcome and latent class.

Treatment characteristics	Total (n = 46,467)	Class 1: <i>Heroin, low poly-substance</i> (n = 25,469)	Class 2: <i>Heroin, crack, alcohol</i> (n = 2496)	Class 3: <i>Heroin, crack</i> (n = 15,566)	Class 4: <i>Heroin, crack, cannabis</i> (n = 2936)
Exposure – interventions received					
Opioid pharmacotherapy, n (%)	36,122 (77.7)	20,377 (80.0)	1602 (64.2)	12,082 (77.6)	2061 (70.2)
Psychosocial interventions, n (%)	25,742 (55.4)	13,682 (53.7)	1537 (61.6)	8694 (55.9)	1829 (62.3)
In-patient withdrawal management, n (%)	3010 (6.5)	1546 (6.1)	275 (11.0)	1021 (6.6)	168 (5.7)
Residential rehabilitation, n (%)	1620 (3.5)	711 (2.8)	167 (6.7)	617 (4.0)	125 (4.3)
Median weeks to discharge					
Successful completion (IQR) ^a	39.5 (15.3–109.9)	46.0 (16.6–119.7)	30.9 (14.9–79.1)	34.1 (14.0–99.3)	31.9 (14.6–90.4)
Died, (IQR)	81.0 (32.0–147.9)	83.4 (35.7–150.0)	51.4 (16.4–177.2)	81.1 (32.0–140.3)	65.3 (11.0–142.1)
Incarcerated, (IQR)	35.4 (14.7–82.6)	38.4 (16.0–85.9)	33.9 (13.3–87.0)	32.3 (13.3–79.0)	34.4 (13.0–73.9)
Unsuccessful transfer, (IQR)	32.4 (12.9–79.3)	35.0 (13.3–84.3)	27.1 (10.3–74.9)	30.7 (12.3–75.6)	27.6 (11.1–66.3)
Dropped out, (IQR)	22.9 (9.9–57.7)	25.1 (10.7–61.9)	19.1 (9.1–46.7)	20.9 (8.9–52.7)	20.3 (9.7–55.9)
Total, (IQR)	31.0 (12.6–80.3)	34.3 (13.3–87.0)	25.6 (11.8–67.9)	28.0 (11.6–73.4)	27.0 (11.9–69.9)
Treatment exit status					
Successful completion, n (%)	13,360 (28.8)	7675 (30.1)	718 (28.8)	4066 (26.1)	901 (30.7)
Died, n (%)	684 (1.5)	435 (1.7)	52 (2.1)	182 (1.2)	15 (0.5)
Incarcerated, n (%)	7425 (16.0)	3820 (15.0)	299 (12.0)	2845 (18.3)	461 (15.7)
Unsuccessful transfer, n (%)	8385 (18.1)	4498 (17.7)	449 (18.0)	2922 (18.8)	516 (17.6)
Dropped out, n (%)	16,613 (35.8)	9041 (35.5)	978 (39.2)	5551 (35.7)	1043 (35.5)
Treatment outcome					
Successful completion and no re-presentation within six months, n (%)	10,194 (21.9)	5882 (23.1)	566 (22.7)	3063 (19.7)	683 (23.3)

Emboldened percentages and means are statistically significant ($P < 0.05$) from multinomial logistic regression (Class 1: referent).^a IQR = interquartile range.

4. Discussion

Over the five-year observation period, we observed that nearly one in three patients successfully completed treatment for OUD. Reinforcing previous research (Luchansky et al., 2000), patients who successfully completed treatment were least likely to be re-admitted to treatment within a subsequent six-month period. In our national population of patients accessing publicly-funded treatment, one in five achieved a sustained benefit from treatment.

Other studies have noted two (Shand et al., 2011), three (Harrell et al., 2012; Monga et al., 2007), five (Kuramoto et al., 2011), or eight (Patra et al., 2009) latent class structures. Our analysis of polydrug dependence in patients seeking treatment for OUD in England revealed a four-class structure. Crack cocaine was a defining characteristic in three of these classes, with one class being further classified with alcohol dependence and another classified with cannabis dependence. It is interesting to note that the only crack cocaine class without alcohol or cannabis dependence had worse outcomes than the heroin with low polydrug class.

4.1. Integration with the literature

Unlike other large-scale studies on treatment completion (Arndt et al., 2013; Mennis and Stahler, 2016), in our unadjusted models patients from Black and Minority Ethnicities (BME) were more likely to recover. After controlling for other socio-economic factors, however, this disparity no longer held, highlighting the importance controlling for employment and stable housing (Saloner and Lê Cook, 2013; Hawkins et al., 2014). Our findings provide general support for the construct of ‘physical capital’ (Cloud and Granfield, 2008) playing a major role in recovery from heroin use disorder, as employment and stable housing were found to significantly affect the likelihood of recovery. The finding that increased time spent engaged in treatment increases the likelihood of successful completion aligns with previous research (Hubbard et al., 2003; Simpson and Sells, 1990) and provides evidence that OUD treatment should not be time-limited (Advisory Council on the Misuse of Drugs, 2014).

After controlling for patient-level and area-level deprivation predictors of outcome, local treatment systems that were performing significantly below the expected rate also appeared to have a much larger opiate using population and, presumably as a result of this, a higher rate of both offending and drug-related deaths. We are not able to determine a mechanism for this association. There may be social network influences in operation. For example, social networks can influence both a transition to injecting heroin (Neaigus et al., 2006) and the decision to share injecting equipment (De et al., 2007). Heroin users who have achieved abstinence often cite moving away from drug-using social networks and receiving support from non-using friends as a contributory factor to their success (Best et al., 2008).

4.2. Strengths and limitations

The main study strength is the national, large scale, long-term follow-up of all individuals accessing treatment for heroin use disorder in England and the utilisation of the national administrative database to monitor relapse. Unlike other comprehensive administrative datasets (Sahker et al., 2015; Alterman et al., 2001; Stahler et al., 2016), NDTMS has patient-level identifiers that enable cross-referencing with subsequent treatment admissions. This utility provides not only an objective summative measure of the sustainability of recovery in this population, it also enables national administrative systems to objectively capture whether patients had previously accessed treatment services, which is an important negative predictor of treatment outcome (Siguel and Spillane, 1978; Marsden et al., 2012).

Several study limitations are also acknowledged: firstly, our analysis of OUD sub-populations is based on clients entering the treatment system in 2008/09. It is possible that since this period, with the rise of novel psychoactive substances for example, a different class structure would emerge for clients currently accessing treatment. Second, we were not able to access data from the national deaths registry or the national prisons system, and there remains a concern that at least some of our patients who did not re-present to treatment were simply unable to. Third, while all available covariates in NDTMS were screened in the present analysis, other covariates could further elucidate the likelihood

Table 4
Unadjusted and multi-level, complete-case and all-case multivariable logistic regression of SCNR outcome.

Covariates	Unadjusted OR (95% CI) (n = 37,460)	Complete-case AOR (95% CI) (n = 37,460)	All-cases AOR (95% CI) (n = 46,467)
<i>Socio-demographic</i>			
Male	0.87 (0.82, 0.92)	0.88 (0.83, 0.94)	0.88 (0.83, 0.93)
Age	1.07 (1.06, 1.09)	1.09 (1.07, 1.11)	1.09 (1.07, 1.11)
BME	1.11 (1.03, 1.20)	1.05 (0.97, 1.14)	1.02 (0.94, 1.09)
Employed	1.46 (1.36, 1.58)	1.24 (1.15, 1.34)	1.27 (1.18, 1.37)
No fixed abode	0.74 (0.70, 0.79)	0.85 (0.80, 0.91)	0.86 (0.81, 0.91)
<i>Deprivation:</i>			
Quintile 2	0.88 (0.80, 0.96)	0.93 (0.84, 1.02)	0.94 (0.86, 1.02)
Quintile 3	0.82 (0.74, 0.90)	0.91 (0.82, 1.00)	0.91 (0.83, 1.00)
Quintile 4	0.79 (0.71, 0.87)	0.84 (0.76, 0.93)	0.86 (0.78, 0.94)
Quintile 5 (highest)	0.63 (0.57, 0.70)	0.74 (0.67, 0.83)	0.77 (0.70, 0.85)
<i>Clinical</i>			
<i>Injecting:</i>			
Previously injected	0.81 (0.76, 0.86)	0.87 (0.81, 0.93)	0.86 (0.81, 0.91)
Currently injector	0.59 (0.55, 0.63)	0.64 (0.60, 0.69)	0.64 (0.60, 0.69)
<i>Referral route:</i>			
Self	0.95 (0.88, 1.01)	0.96 (0.90, 1.03)	0.97 (0.92, 1.04)
Criminal justice	0.58 (0.54, 0.63)	0.68 (0.63, 0.74)	0.68 (0.63, 0.73)
<i>Drug use class:</i>			
Class 2: Heroin, crack & alcohol	0.92 (0.81, 1.03)	1.02 (0.90, 1.15)	0.97 (0.87, 1.08)
Class 3: Heroin & crack	0.82 (0.77, 0.87)	0.92 (0.86, 0.98)	0.90 (0.85, 0.95)
Class 4: Heroin, crack & cannabis	0.99 (0.89, 1.11)	1.08 (0.97, 1.20)	1.02 (0.92, 1.12)
Previously treated	0.64 (0.61, 0.67)	0.66 (0.62, 0.69)	0.66 (0.63, 0.70)
Heroin career	0.99 (0.97, 1.00)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)
<i>Time in index treatment journey:</i>			
6 months to < 1 year	1.28 (1.19, 1.39)	1.28 (1.19, 1.38)	1.32 (1.23, 1.41)
1 year to < 2 years	1.43 (1.33, 1.55)	1.40 (1.29, 1.51)	1.39 (1.30, 1.49)
2 years to 5 years	2.70 (2.51, 2.90)	2.59 (2.41, 2.79)	2.60 (2.43, 2.78)
<i>Model statistics</i>			
Constant	–	0.38 (0.33, 0.43)	0.39 (0.34, 0.44)
Wald χ^2 (d.f. = 21)	–	1538	1834–1854
LR test χ^2 (d.f. = 2)	–	938	1342–1349
<i>Random effects parameters (ICC):</i>			
Treatment system (Level 3)	–	0.01 (0.00, 0.02)	0.17 (0.11, 0.27)
Treatment agency (Level 2)	–	0.13 (0.11, 0.15)	0.13 (0.11, 0.15)

SCNR, 'successful completion of treatment journey and no representation to treatment within six months'; OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval; d.f., degrees of freedom; ICC, intra-class correlation coefficient.

Emboldened percentages and means are statistically significant ($P < 0.05$).

of sustaining recovery, including treatment motivation (Simpson and Joe, 1993), engagement (Simpson et al., 1995) and other recovery strengths (Gossop et al., 2002). Fourth, it is possible that other interventions were experienced by the patients in this cohort, such as privately-funded residential treatment or attending Alcoholics Anonymous, but these interventions are not captured by NDTMS and it is not possible to assess the potential impact these may have had.

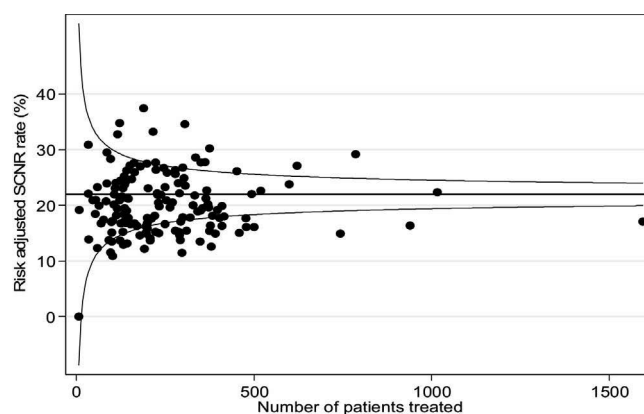


Fig. 1. Funnel plot of outcome performance (SCNR rate) by local treatment system.

NB: The horizontal line is the national average for the SCNR outcome. The curved lines are the upper and lower 95% confidence interval. Each black dot represents a local treatment system. Local systems lying above the upper CI have an SCNR outcome performance that is better than average after risk-adjustment. Local systems lying below the lower CI have an SCNR outcome performance that is worse than average after risk-adjustment.

4.3. Conclusions

Relapse requiring treatment is relatively common in the six months following treatment completion. This study highlights the importance of including re-presentation to treatment as a summative measure of the effectiveness of local treatment systems. We note a sizeable proportion of individuals, nearly one in seven, who have been continuously engaged in treatment throughout the five-year observation period. The next questions for our research group are whether, and to what degree, heroin and other drug use changes throughout this time period; how change in heroin use relates to change in other drugs; whether five-year in-treatment change predicts subsequent successful completion of treatment, and to examine the longitudinal inter-relationship between substance use, employment and housing.

Conflict of interest declarations

B.E. is employed with the Evidence Application Team within the Alcohol, Drug and Tobacco Division, Health and Wellbeing Directorate, Public Health England. He is enrolled on a part-time PhD programme at King's College London.

J.S. a researcher and clinician who has worked with a range of types of treatment and rehabilitation service-providers. J.S. is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London. He has also worked with a range of governmental and non-governmental organisations, and with pharmaceutical companies to seek to identify new or improved treatments from whom he and his employer (King's College London) have received honoraria, travel costs and/or consultancy payments. This includes work with, during past 3 years, Martindale, Reckitt-Benckiser/Indivior, MundiPharma, Braeburn/MedPace and trial medication supply from iGen. His employer (King's College London) has registered intellectual property on a novel buccal naloxone formulation and he has also been named in a patent registration by a Pharma company as inventor of a concentrated nasal naloxone spray. For a fuller account, see JS's web-page at <http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx>.

J.M. is a clinical research psychologist and cognitive behavioural psychotherapist. He works in an integrated university and National Health Service academic health sciences centre (Institute of Psychiatry, Psychology and Neuroscience [IoPPN], King's College London [KCL]) and King's Health Partners). He is supported by research grants from

Table 5
Population estimates by local treatment system outcome performance, England.

Estimates	All local systems (n = 149)	Performance better than expected (n = 14)	Performance worse than expected (n = 38)	Incidence rate difference
Median of population aged 16–64 (interquartile range) ^a	172,000 (127,100–272,700)	210,550 (171,250–433,725)	170,100 (140,625–219,725)	–
Number of opiate users per 1000 (95% CI) ^a	7.7 (6.5–9.0)	6.3 (5.0–7.6)	10.4 (9.1–11.9)	4.1 (4.0–4.2)
Offence rate per 1000 (95% CI) ^b	106.3 (106.2–106.4)	97.5 (97.2–97.8)	126 (125.7–126.2)	28.5 (28.1–28.8)
Drug-related deaths per million (95% CI) ^c	33.5 (32.7–34.4)	32.9 (30.2–35.8)	38.8 (36.9–40.8)	5.9 (5.9–5.9)

^a (Hay et al., 2010).

^b (Office for National Statistics, 2016).

^c (Public Health England, 2016b).

the Department of Health, Institute for Health Research (NIHR), and the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Mental Health Foundation Trust (SLaM MHFT). He declares part-time employment as Senior Academic Advisor for the Alcohol, Drugs and Tobacco Division, Health and Wellbeing Directorate, Public Health England and untied education grant funding from the pharmaceutical industry at IoPPN and SLaM MHFT for a study of psychological interventions in opioid maintenance (2010–2016; Indivior PLC via Action on Addiction) and honoraria from Merck Serono in 2013 and 2015 (oncology medicine), and Indivior via PCM Scientific (co-chair of the Improving Outcomes in Treatment of Opioid Dependence conference, 2015). He holds no stocks in any company.

Role of funding source

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Contributors

The design and statistical analysis plan for this study was developed and implemented by B.E. and J.M. B.E. and J.M. wrote the first draft of the manuscript. Following input from J.S., B.E., J.M. wrote a further draft of the manuscript and B.E. then took the decision to submit for publication. All authors approved of the manuscript before submission.

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Full length article

Continuous opioid substitution treatment over five years: Heroin use trajectories and outcomes

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ABSTRACT

Background: This is the first national study in England of continuous long-term opioid substitution treatment (OST).**Methods:** All adults were admitted to community OST for opioid use disorder (OUD) in 2008/09 with continuous enrolment to 2013/14 ($n = 7719$). Heroin use trajectories were identified by multilevel Latent Class Growth Analysis. In Year 6 and 7 of follow-up, the outcome measure (analysed by multilevel, multivariable logistic regression) was 'successful completion and no re-presentation' (SCNR) to community treatment within six months.**Results:** Five heroin use trajectory classes were identified: 'gradual decreasing' (20.9%), 'decreasing then increasing' (21.7%), 'continued low-level' (17.0%), 'rapid decreasing' (25.6%), and 'continued high-level' (14.8%). At the end of Year 7, 4616 people (60.3%) remained in OST. Of those discharged, 28.8% achieved the SCNR follow-up outcome. SCNR was more likely in the 'gradual decreasing' (adjusted odds ratio [AOR] 2.40; 95% confidence interval [CI] 1.77–3.26), 'continued low-level' (AOR 2.46; CI 1.78–3.40), and 'rapid decreasing' (AOR 3.40; CI 2.43–4.37) classes relative to the 'continued high-level' class. SCNR was more likely among patients employed at admission (AOR 1.45; 95% CI 1.15–1.83) and those receiving adjunctive psychosocial interventions (AOR 1.44; 95% CI 1.03 to 2.02).**Conclusions:** Among English patients in OST for 5 years, heroin use trajectories were clearly delineated with a gradient of response on the study outcome. Successful completion and no re-presentation was achieved by 28.8% of discharged patients. The rapid decreasing trajectory had the greatest likelihood of positive outcome. Adjunctive psychosocial intervention during OST was associated with positive outcome.

1. Introduction

Oral methadone or buprenorphine are the first-line medical therapies for opioid use disorder (OUD). These opioid substitution treatments (OST) are consistently associated with abstinence from illicit opioid use (e.g., Hubbard et al., 2003; Gossop et al., 2003; Teesson et al., 2006), a lowered risk of opioid overdose (White et al., 2015), and reductions in criminal behaviour (Gossop et al., 2005). Aggregate statistical results may, however, mask differential clinical response among sub-populations. For example, in an English national study of ongoing OUD treatment, 37% of patients were abstaining from heroin during the 28 days before six-month follow-up; a further 31% were using heroin less often, but 29% continued to use heroin at the same frequency as at

admission, and 3% had deteriorated (Marsden et al., 2009).

Longer follow-up studies have identified distinct sub-populations of people who share a similar heroin use trajectory. In a US cohort study of 471 heroin users followed-up over 16 years, Hser and colleagues identified three classes: nine per cent were 'early-quitters', 32% achieved improvements at a later stage in follow-up ('late-decelerated users'), and 59% were labelled 'stably high-level' heroin users with no identifiable improvement (Hser et al., 2007). In a recent 4.5-year follow-up of study of 795 participants in a treatment trial, Hser's group identified the following classes: 'low use' (42.0%), 'high use' (22.3%), 'decreasing use' (18.6%), and 'increasing use' (17.1%), with people in the 'decreasing use' class spending more time in treatment than those in the 'high use' class (Hser et al., 2017). Comparable findings have been

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reported in Australia (Teesson et al., 2017).

Recently, we estimated the likelihood of successfully completing OUD treatment within five years among a national cohort of adult patients admitted to public treatment services in 2008/09 ($N = 54,357$; Eastwood et al., 2017). Approximately 1:7 patients were continuously enrolled in OST at the end of the five-year observation period. In the present study, we report on the follow-up outcomes of this cohort over the next two years. This is the first national outcome study of long-term continuous OST in England. To our knowledge, there has been no national study of OST over this time-frame reported elsewhere.

In this report, we aim to: (1) identify heroin use response trajectories during five years of OST and estimate associations with patient-level characteristics and treatment exposure and (2) estimate whether heroin use response trajectories predict positive outcome during the sixth and seventh year of follow-up.

We hypothesised that: (a) patients with trajectories demonstrating positive response to ongoing OST would be more likely to exit treatment successfully, and (b) adjunctive psychosocial, in-patient, and residential interventions would increase the likelihood of completing OST successfully.

2. Methods

2.1. Design

This was a seven-year, prospective, observational cohort study of all publicly-funded specialist community-setting treatment services providing OST in England reporting to the National Drug Treatment Monitoring System (NDTMS). The study is reported following the RECORD guidelines for observational research using routinely collected health data (Benchimol et al., 2015).

The study cohort is all adults (≥ 18 years; $n = 7877$) diagnosed with OUD (almost all relating to use of heroin) who initiated treatment between 1 April 2008 and 31 March 2009, were continuously enrolled in OST for the next five years (ending 31 March 2014), and then followed-up to 30 September 2016. Following the NDTMS reporting protocol, ‘continuous enrolment’ was defined as either a single unbroken episode of OST or two or more linked (continuing care) episodes in which there was no more than 21 days between the end of one methadone or buprenorphine prescribing intervention and the start of another (Public Health England, 2015).

2.2. Measures

2.2.1. Developmental trajectory indicator

The Treatment Outcomes Profile (TOP; Marsden et al., 2008) is the English national standard tool for substance use disorder treatment outcomes monitoring. The TOP is a structured clinical interview that is completed at admission, every six months thereafter, and at the completion of treatment. In this study, we used the number of days of heroin use in the 28 days prior to each TOP interview conducted between Year 1 (2008/09) and Year 5 (2013/14).

2.2.2. Outcome measure

‘Successful completion’ of treatment has been widely used as an outcome measure in effectiveness studies. Definitions vary, but this typically denotes satisfactory resolution of primary clinical problems and agreement between the clinician and patient to exit treatment (e.g., Luchansky et al., 2000; Alterman et al., 2001; Stahler et al., 2016).

The outcome measure in the present study combined two components: successful completion and no re-presentation (SCNR). SCNR is the English national proxy remission measure for OUD treatment outcome monitoring (Public Health England, 2015). The ‘successful completion’ component was measured in Year 6 and Year 7 (ending 31 March 2016). It was defined as a clinician-verified report of a patient who had completed OST, was in remission from OUD, was abstinent

from heroin (and any other non-medical opioids) and cocaine, and had attained their care plan goals. The ‘no re-presentation’ element captures the extent to which the successful completion is sustained by linking patients with a successful completion to the community-based and prison-based treatment databases, as well as the Office for National Statistics’ fatal drug-poisoning database over the subsequent six-month period (ending 30 September 2016), and removing all cases of re-presentation to treatment or fatal overdose from the summative effectiveness measure.

2.2.3. Baseline covariate measures

The following patient demographic, clinical, and previous treatment exposure variables (all recorded at initial assessment) were included as potential confounders in the analysis.

2.2.3.1. Demographics. Demographics measured were: sex; age (centred at 18 years and utilised in five-year increments); Black and Minority Ethnicities (BME: a legal monitoring requirement (Race Relations (Amendment) Act, 2000); whether employed; housing problems (defined primarily as having no fixed abode, but can also include squatting, short-term hostel/B and B, staying with friends/relatives [homeless, herein]).

2.2.3.2. Social deprivation. Local area deprivation was measured by the English Indices of Multiple Deprivation (IMD; Department for Communities and Local Government, 2007). IMD data were linked to NDTMS based on the patient’s residential postcode district or the location of their first treatment provider in instances of missing postcode information.

2.2.3.3. Treatment admission drug use latent class. Four heroin-based latent classes from admission data were used: (1) heroin low level with concurrent drug disorder, (2) heroin, crack and alcohol, (3) heroin and crack, and (4) heroin, crack and cannabis. These classes were identified in Eastwood et al. (2017).

2.2.3.4. Injecting status. Recorded at the start of treatment as (1) never injected, (2) lifetime history of injecting, and (3) current injector.

2.2.3.5. Duration of heroin use ‘career’. This was defined as the number of years between first initiation to heroin use and initiating OUD treatment. In the models, this variable was mean centred and utilised in five-year increments.

2.2.3.6. Treatment history. The patient’s referral route into treatment was categorised as (1) self-referred, (2) criminal-justice system, or (3) other. Whether a patient had previously accessed OUD treatment was also included.

2.2.3.7. Adjunctive treatment exposure. Together with OST, NDTMS records the following interventions: psychosocial interventions, in-patient detoxification, and residential rehabilitation.

2.3. Statistical analysis

Data management was done with SPSS (version 21). We used multilevel Latent Class Growth Analysis (LCGA) to identify discrete, non-overlapping heroin use change trajectories across five years of OST (MPlus; version 7). Management of missing data by multiple imputation and all regression analyses were done with Stata (version 13).

2.3.1. Heroin use trajectories

In a longitudinal latent analysis of behaviour change, trajectory membership can be influenced by inclusion of covariates and distal outcomes (Huang et al., 2010). Following recommendation by Nagin (2005), 1-class through 6-class models were fit to the data. Each model

assumed a Poisson distribution, and 5000 random sets of starting values were used to guard against convergence on local maxima (McLachlan and Peel, 2000). A minimum class size of 5% was set for utility (Borders and Booth, 2012; Willey et al., 2016).

Trajectory identification was informed by posterior fit statistics. As patients were nested within different local treatment systems, we used multilevel LCGA models, and an intra-class correlation coefficient (ICC) was computed for each class (Asparouhov and Muthén, 2007). Multinomial logistic regression then regressed trajectory classes on patient-level characteristics. Robust standard errors were utilised to calculate 95% confidence intervals (CI) to account for clustering of patients in each treatment system.

2.3.2. Outcome analysis

A multilevel, multivariable logistic regression model was used to estimate the likelihood of SCNR (Stata command: *meqrlogit*), and the ICC was estimated to assess intercept variation. As a sensitivity analysis, we calculated the E-value from the adjusted odds ratios of the LCGA trajectories and the estimate of its uncertainty from the CIs closest to the null. In this application, the E-value is the minimum strength needed by an unmeasured confounder to account for any significant association between trajectory membership and outcome conditional on the included covariates (VanderWeele and Ding, 2017).

2.3.3. Missing data

LCGA is implemented by full-information maximisation likelihood and can assign patients with at least one measurement to a latent class. However, a complete case analysis may yield biased estimates due to missing covariate data. With no evidence that either the predictors or outcome variables were not missing-at-random (Little and Little, 2002), we created a multiply imputed dataset (Stata command: *MI impute chained*). Logistic regression, multinomial regression, and predictive mean matching were utilised, respectively, for binary, multinomial, or continuous covariates with missing data. Twenty probabilistic datasets were imputed, resulting in a relative efficiency of over 98% (Rubin, 1987) and a reduction in power of less than 1% (Graham et al., 2007).

3. Results

3.1. Study cohort

Patients were recruited from all 149 local treatment systems in England (median 41; interquartile range [IQR] 23–71).

The flow of the 7877 participants continuously enrolled in OST for five years is shown in Fig. 1. Two percent of the cohort ($n = 158$) had no TOP data and were removed. Therefore, LCGA was undertaken on 7719 cases. A median of 10 TOP interviews were completed (IQR 8–11), and 2211 patients (28.6%) completed all 11 TOP assessments. A further 58 people (0.7%) were removed, as their follow-up status could not be determined.

At the end of Year 7, 4616 (60.3%) were still enrolled in OST. During Year 6 and 7, 1987 (25.9%) exited treatment unsuccessfully, and 1058 (13.8%) successfully completed treatment. Among those successfully completing treatment, 16.5% ($n = 175$) were re-admitted to community treatment in the next six months, five were incarcerated, and one person died from opioid-related poisoning.

The ‘successful completion and no re-presentation’ (SCNR) outcome was achieved by 877 (28.8%) of those discharged from OST ($n = 3045$).

3.2. Heroin use during five years of OST

Heroin use was reported by 85.8% of the cohort during the 28-days before the start of treatment (Table 1). Proportionately, the greatest reduction in heroin was in the first six months of OST, at which point 62.7% were still using. Overall, 39.6% of the cohort were using heroin

at Year 3, and there was a slight increase at each six-monthly assessment to Year 5 (43.2%). The mean number of days used reduced from 19.5 days at intake to 7.4 days at six months and did not exceed four days after 2.5 years in treatment. Correlations over follow-up are shown in Supplementary Material (Table S1¹).

3.3. Heroin use trajectories

Table 2 displays the results of the multilevel LCGA models. Model indicators pointed to a 6-class solution. However, two classes had consistently low heroin use over the five years. Accordingly, we judged a parsimonious 5-class model to be optimal. The ICC for classes 1, 2, 4 and 5 ranged between 0.46 and 0.49 and was 0.04 for class 3.

We labelled the heroin use trajectory classes as follows (Fig. 2):

- Class 1 ($n = 1617$, 20.9%: ‘gradual decreasing’)
- Class 2 ($n = 1673$, 21.7%: ‘decreasing then increasing’)
- Class 3 ($n = 1310$, 17.0%: ‘continued low-level’)
- Class 4 ($n = 1973$, 25.6%: ‘rapid decreasing’)
- Class 5 ($n = 1146$, 14.8%: ‘continued high-level’)

3.4. Patient-level characteristics

Patient-level characteristics are shown in Table 3 together with the results of the all-case multinomial logistic regression of the heroin use trajectory classes on patient-level characteristics. Compared to the poor response (‘continued high-level’) class, participants in the other classes had less previous OUD treatment exposure, and the ‘decreasing then increasing’, ‘continued low-level’, and ‘rapid decreasing’ classes were less likely to be currently injecting at admission.

The ‘decreasing then increasing’ heroin use class had more men, and they were less likely to reside in an area of high social deprivation. The ‘continued high-level’ heroin use class were more likely to be exposed to psychosocial, in-patient, and residential treatments during their enrolment in OST.

3.5. Treatment status at the end of year 7

Continued enrolment in OST at the end of Year 7 was not associated with heroin use trajectory (Table 4). Among the treatment leavers, the ‘continued high-level’ heroin users were most likely to have an unsuccessful discharge. There was an outcome response gradient by class among those who left treatment successfully: successful completion of treatment was recorded for 8.6% of the ‘continued high-level’ class compared to 18.7% of the ‘rapid-decreasing’ class. Patients who continuously enrolled at Year 7 were removed from further analysis at this point.

Compared to the ‘rapid decreasing’ heroin use class (re-admission rate 11.2%), re-presentation within six months for community treatment was more likely among the ‘continued high-level’ heroin use class (22.4%; odds ratio [OR] 2.29; 95% CI 1.29–4.08); this was followed by the ‘decreasing then increasing’ class (22.2%; OR 2.26; 95% CI 1.38–3.71), the ‘gradual decreasing’ class (17.3%; OR 1.72; 95% CI 1.08–2.73), and the ‘continued low-level’ class (17.8%; OR 1.66; 95% CI 1.01–2.72).

3.6. Impact of trajectory membership on outcome

The poor responding ‘continued high-level’ heroin using class had the lowest proportion achieving SCNR (16.2%), followed by the ‘decreasing then increasing’ group (19.6%). The ‘continued low-level use’ and ‘gradual decreasing use’ groups had similar levels of SCNR (31.2%

¹ Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

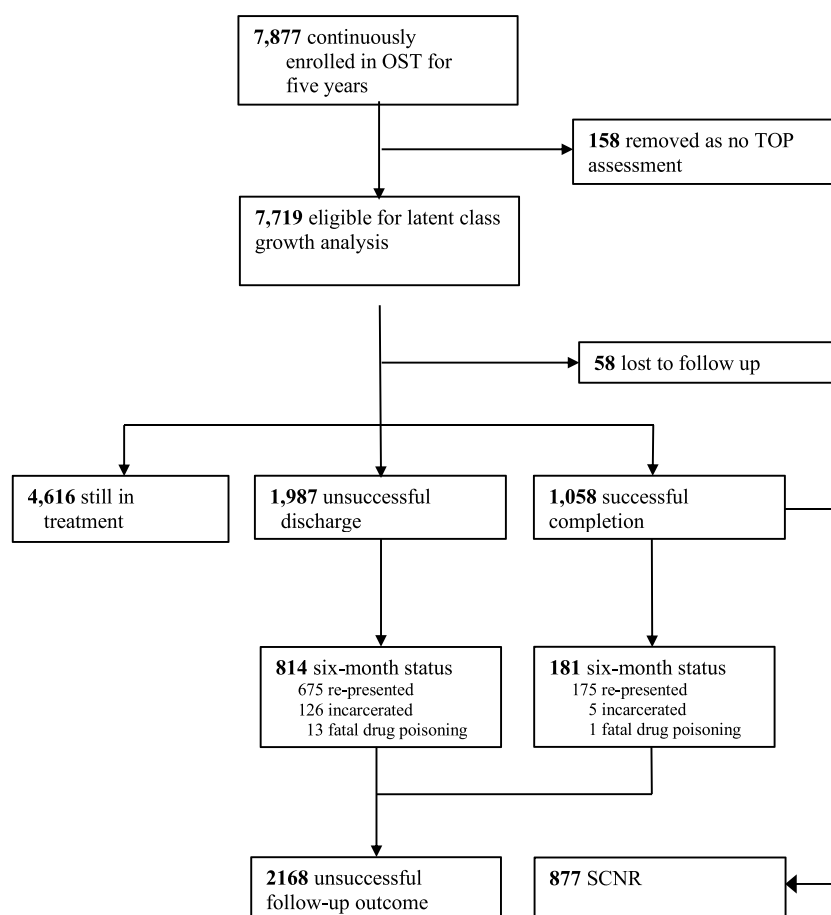


Fig. 1. Study profile.

Table 1

Heroin use during five years of continuous OST (n = 7719).

TOP assessment	Responses (n)	No. (%) using heroin	Mean days used (SD)*
Admission	5,567	4,775 (85.8)	19.5 (11.6)
Year 0.5	5,774	3,622 (62.7)	7.4 (9.7)
Year 1	6,409	3,796 (59.2)	6.0 (8.7)
Year 1.5	6,449	3,673 (57.0)	5.9 (8.6)
Year 2	6,567	3,498 (53.3)	5.4 (8.3)
Year 2.5	6,649	2,899 (43.6)	4.0 (7.5)
Year 3	6,670	2,639 (39.6)	3.5 (6.9)
Year 3.5	6,713	2,729 (40.7)	3.7 (7.1)
Year 4	6,733	2,821 (41.9)	3.6 (7.30)
Year 4.5	6,743	2,873 (42.6)	3.9 (7.2)
Year 5	6,748	2,913 (43.2)	4.0 (7.4)

TOP = Treatment Outcomes Profile.

SD = standard deviation.

* Mean days of opioid use in past 28 days.

and 31.7%, respectively), while SCNR was most likely to be attained by the 'rapid decreasing' class (39.7%).

The multiply imputed, multilevel logistic regression analysis (Table 5) indicated that three trajectory groups (i.e., 'gradual decreasing', 'continued low-level', and 'rapid decreasing') were more likely to achieve SCNR compared to the 'continued high-level' class (adjusted odds ratio [AOR] 2.40 [95% CI 1.77–3.26]; AOR 2.46 [95% CI 1.78 to 3.40]; AOR 3.26 [95% CI 2.43 to 4.37]), respectively.

The E-value estimate for the 'gradual decreasing' class was 4.23 (with an uncertainty estimate of 2.94 for the minimum risk ratio needed to shift the CI to the null), E = 4.36 (uncertainty estimate = 2.96) for the 'continued low-level use' class, and E = 5.97 (uncertainty

estimate = 4.29) for the 'rapid decreasing use' class. There was also an increased likelihood of achieving SCNR among those with pre-admission employment (AOR 1.45; 95% CI 1.15 to 1.83) and those who received adjunctive psychosocial treatment during OST (AOR 1.44; 95% CI 1.03 to 2.02) and a positive association for increasing age (AOR 1.07; 95% CI 1.00 to 2.14). Longer heroin using career, lifetime history of injecting, and referral from the criminal justice system was associated with a decreased likelihood of achieving SCNR.

3.7. Post-hoc analysis

Finally, we created a binary 'non-response' measure by combining the 'continued high-level use' and 'decreasing then increasing use' trajectory groups against the remaining three trajectory groups. This measure was then collapsed at the local treatment system level resulting in a range of non-response from 0 to 70%. Also available at local area level were the prevalence of opiate users per 1000 population in 2008/09 (Hay et al., 2010), the rate of offending per 1000 population (Office for National Statistics, 2016), and the rate of drug-related deaths per million population (Public Health England, 2016). Non-response was regressed on these three measures in a linear regression. The offending rate and the drug-related death rate were not associated with non-response. However, for every extra opiate user per 1000 population there was an increase in non-response by almost two percentage points (1.97; 95% CI 0.76 to 3.17).

4. Discussion

In a time of increased focus on recovery (Home Office of the United Kingdom Government, 2017; Laudet and Humphreys, 2013), a greater

Table 2
Unconditional multilevel latent class growth analysis of heroin use over five years (n = 7719).

	1-Class	2-Class	3-Class	4-Class	5-Class	6-Class
AIC	886002.87	671087.82	610578.39	580090.68	553248.75	537428.48
BIC	886023.73	671136.50	610654.88	580194.97	553380.86	537588.40
aBIC	886014.20	671114.25	610619.92	580147.31	553320.48	537515.31
Entropy	–	0.975	0.971	0.964	0.950	0.956
Class (probability)						
Class 1	1.00 (1.00)	0.58 (0.99)	0.42 (0.99)	0.24 (0.97)	0.21 (0.97)	0.12 (0.96)
Class 2	–	0.42 (0.99)	0.21 (0.99)	0.37 (0.99)	0.22 (0.97)	0.25 (0.97)
Class 3	–	–	0.37 (0.99)	0.23 (0.97)	0.17 (0.97)	0.18 (0.97)
Class 4	–	–	–	0.16 (0.99)	0.26 (0.94)	0.14 (0.98)
Class 5	–	–	–	–	0.15 (0.98)	0.17 (0.96)
Class 6	–	–	–	–	–	0.15 (0.95)
VLMR	–	< 0.01	0.12	< 0.01	< 0.01	< 0.01
BLRT	–	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; aBIC: sample-size adjusted BIC; VLMR: Vuong-Lo-Mendel-Ruben test; BLRT: bootstrapped likelihood ratio test.

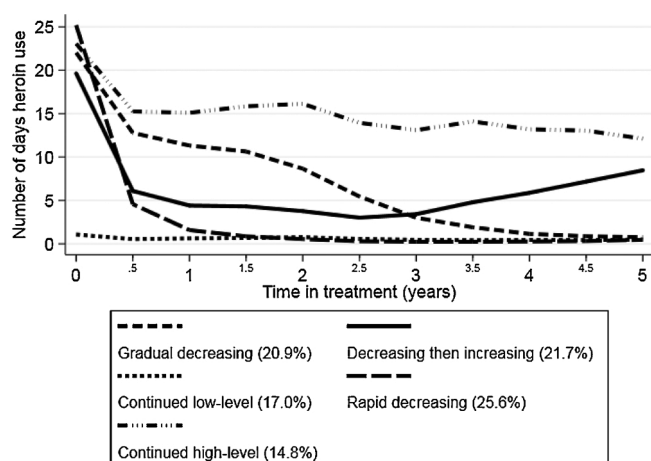


Fig. 2. Heroin use trajectories over 5 years of continuous OST.

understanding of the heterogeneous response to treatment is required by policy makers, treatment purchasers, and clinicians to inform their decision-making processes. This report extends our previous study (Eastwood et al., 2017) by estimating heroin use change trajectories over long-term enrolment in OST. We identified five heroin use trajectory groups and found that the trajectory groups tending towards abstinence at Year 5 were significantly more likely to achieve a sustained benefit from treatment (SCNR follow-up outcome).

4.1. Integration with the literature

In the treatment literature, several demographic and patient-level characteristics have been linked to developmental trajectories associated with relatively poor treatment response, including: males, people from some ethnic minorities, lower educational achievement, earlier onset of drug use, and involvement with the criminal justice system (Grella and Lovinger, 2011; Hser et al., 2008, 2007).

Our ‘continued low-level’, ‘continued high-level’, and ‘decreasing then increasing’ classes are similar to the ‘low use’, ‘high use’, and ‘increasing use’ response groups identified by Hser’s group (Hser et al., 2008). Other studies have also highlighted a sub-population that does not exhibit substantial reduction in drug use as well as a group demonstrating rapid reductions (Grella and Lovinger, 2011; Teesson et al., 2017). This points to a degree of phenotypic similarity across different countries, settings, and cohort characteristics. Similar to the Australian study (Teesson et al., 2017), we note that few baseline covariates predict trajectory membership, although higher deprivation, currently injecting, and previous treatment were associated with relative non-

response to treatment.

The validity of person-centred latent trajectory modelling has been criticised (Sher et al., 2011). Our finding that more favourable trajectory memberships are associated with sustained benefit provides support for the predictive validity of the approach. It also extends previous work documenting associations with decreased mortality and better employment, substance use, and mental health outcomes (Hser et al., 2007; Teesson et al., 2017; Hser et al., 2017) and highlights the importance of incorporating independent outcomes in person-centred research design.

Our findings also highlight the positive role of employment in recovery, although it is interesting that stable housing did not affect the likelihood of recovery as in other studies (e.g., Cloud and Granfield, 2008). Injecting and criminal justice referrals were, as expected (Marsden et al., 2012), negatively associated with positive outcome.

4.2. Clinical implications

In our study, we estimate that one in seven patients demonstrate sustained non-response over significant periods of time, and a further fifth of patients exhibit a tendency to deteriorate after three years of treatment. Continued illicit opioid use on top of an opioid prescription is a recognised problem (Clinical Guidelines on Drug Misuse and Dependence Update 2017). It is important for clinicians to identify non-response at an early stage and to review and optimise the treatment care package. Several clinical responses are available, including: increasing the dose, dividing the dose into smaller daily doses in the case of faster metabolism, offering to change the OST medication, and re-introducing daily supervised consumption (ibid). Service user views on medication should be taken into account, as a quarter consider the OST dose to be ‘poor or bad’ (Advisory Council on the Misuse of Drugs, 2015). In the US, around a quarter of patients also receive methadone doses too low to be effective (D’Aunno et al., 2014).

4.3. Policy implications

Our finding that more than 40% of patients continue to use illicit opioids after five years of continuous treatment supports the conclusion that a blanket time limit on prescribing would not be clinically appropriate (Advisory Council on the Misuse of Drugs, 2014). National drug treatment administrators should make available performance monitoring reports for clinics and treatment purchasers focused on long-term use of illicit opioids, which could aid local planning and resource allocation and improve outcomes. Further, incorporation of prescription dose into the NDTMS would help estimate whether, and to what degree, sub-optimal dosing is associated with continued use on top of that dose.

Table 3
Patient-level characteristics by heroin use trajectories (n = 7719).

Covariate	Total	Continued high-level (n = 1146)	Decreasing then increasing (n = 1673)	Continued low-level (n = 1310)	Gradual decreasing (n = 1617)	Rapid decreasing (n = 1973)
Male	5,562 (72.1)	(72.2)	(75.2)	(72.7)	(70.5)	(70.1)
Age ^a	34.4 (7.9)	34.2 (7.4)	33.9 (7.5)	35.2 (8.3)	33.7 (7.8)	34.9 (8.2)
Black/Minority Ethnic	718 (9.3)	(8.4)	(9.7)	(8.5)	(8.7)	(10.5)
Employed ^b	1,164 (15.7)	(13.7)	(16.9)	(13.3)	(14.1)	(18.5)
Homeless ^c	1,775 (23.4)	(25.4)	(23.7)	(20.6)	(26.1)	(21.5)
Social deprivation:						
Quintile 1 (lowest)	1935 (25.1)	(23.6)	(25.5)	(25.9)	(25.2)	(24.9)
Quintile 2	1,562 (20.2)	(19.0)	(20.1)	(18.9)	(18.6)	(23.3)
Quintile 3	1,434 (18.6)	(18.1)	(19.4)	(18.2)	(19.2)	(17.9)
Quintile 4	1,595 (20.7)	(20.9)	(21.2)	(20.0)	(21.3)	(20.1)
Quintile 5 (highest)	1,193 (15.5)	(18.5)	(13.8)	(17.0)	(15.7)	(13.8)
Heroin career ^{a,d}	12.3 (7.7)	12.3 (7.2)	11.9 (7.2)	13.3 (8.0)	11.9 (7.4)	12.5 (8.2)
Drug injecting: ^e						
Never	2,290 (29.9)	(25.4)	(31.5)	(27.7)	(27.9)	(34.3)
Lifetime	2,976 (38.9)	(33.3)	(36.6)	(34.5)	(35.7)	(36.5)
Current	2,387 (31.2)	(41.3)	(31.9)	(17.8)	(36.4)	(29.2)
Referral source:						
Other	2,964 (38.4)	(32.6)	(37.2)	(49.5)	(36.2)	(37.2)
Self	3,244 (42.0)	(46.3)	(44.3)	(26.8)	(43.5)	(46.6)
Criminal justice	1,511 (19.6)	(21.2)	(18.5)	(23.7)	(20.3)	(16.2)
Previous OUD treatment	4,871 (63.1)	(72.8)	(64.4)	(59.4)	(65.9)	(56.6)
Drug use sub-population:						
Heroin low-level concurrent	4,295 (55.6)	(55.2)	(56.6)	(53.4)	(54.9)	(57.1)
drug use disorder						
Heroin, crack and alcohol	388 (5.0)	(4.9)	(5.1)	(4.6)	(6.3)	(4.3)
Heroin and crack	2,589 (33.5)	(34.8)	(32.6)	(36.0)	(32.8)	(32.5)
Heroin, crack and cannabis	447 (5.8)	(5.1)	(5.7)	(6.0)	(5.9)	(6.1)
Adjunctive treatment exposure:						
Psychosocial	7,121 (92.3)	(95.0)	(93.0)	(90.5)	(93.9)	(89.8)
In-patient	566 (7.3)	(11.4)	(7.2)	(5.3)	(8.8)	(5.2)
Residential	109 (1.4)	(3.0)	(1.9)	(0.9)	(1.2)	(0.6)

Figures in parentheses in table are number of participants (percentages) unless otherwise stated.

Emboldened percentages and means are statistically significant ($P < 0.05$) from all-case, multiply imputed, multivariable multinomial logistic regression (continued high-level use group as referent).

^a Year (SD).

^b Percentage after excluding 286 participants with missing data on this covariate.

^c Percentage after excluding 123 participants missing data on this covariate.

^d Percentage after excluding 261 participants missing data on this covariate.

^e Percentage after excluding 66 participants missing data on this covariate.

Table 4
OST status at Year 7, by heroin use trajectory (n = 7661).

Heroin use trajectory class	Still enrolled	Unsuccessful discharge	Successful completion
Continued high-level (n = 1142)	678 (59.4)	366 (32.1)	98 (8.6)
Decreasing then increasing (n = 1660)	1016 (61.2)	482 (29.0)	162 (9.8)
Continued low-level (n = 1298)	803 (61.9)	304 (23.4)	191 (14.7)
Gradual decreasing (n = 1604)	975 (60.8)	388 (24.2)	241 (15.0)
Rapid decreasing (n = 1957)	1144 (58.5)	447 (22.8)	366 (18.7)
Total	4616 (60.3)	1987 (25.9)	1058 (13.8)

Numbers in parentheses are percentages.

Table 5
Unadjusted and multi-level, all-case multivariable logistic regression of SCNR outcome (n = 3045).

Covariate	Unadjusted OR (95% CI)	All-case AOR (95% CI)
Male	0.90 (0.75, 1.07)	0.95 (0.79, 1.15)
Age	1.03 (0.98, 1.08)	1.07 (1.00, 1.14)
Black/Minority Ethnic	1.03 (0.78, 1.36)	0.94 (0.70, 1.26)
Employed	1.61 (1.29, 1.99)	1.45 (1.15, 1.83)
Homeless	0.79 (0.66, 0.96)	0.88 (0.72, 1.08)
Social deprivation		
Quintile 1 (lowest)	1.06 (0.84, 1.35)	1.07 (0.83, 1.37)
Quintile 2	0.78 (0.60, 1.00)	0.84 (0.64, 1.09)
Quintile 3	0.86 (0.67, 1.10)	0.94 (0.73, 1.22)
Quintile 4	0.82 (0.62, 1.09)	0.89 (0.67, 1.20)
Quintile 5 (highest)	–	–
Heroin career	0.95 (0.90, 1.01)	0.93 (0.87, 1.00)
Drug injecting:		
Never	–	–
Lifetime	0.71 (0.58, 0.86)	0.79 (0.64, 0.97)
Current	0.65 (0.53, 0.80)	0.80 (0.64, 1.00)
Referral source:		
Other	–	–
Self	0.92 (0.77, 1.10)	0.94 (0.78, 1.14)
Criminal justice	0.62 (0.50, 0.79)	0.68 (0.54, 0.87)
Previous OUD treatment	0.73 (0.62, 0.86)	0.87 (0.73, 1.03)
Drug use classification:		
Heroin low level concurrent drug disorder	–	–
Heroin, crack and alcohol	1.05 (0.72, 1.54)	1.02 (0.69, 1.51)
Heroin and crack	1.01 (0.85, 1.20)	0.99 (0.83, 1.19)
Heroin, crack and cannabis	0.93 (0.65, 1.33)	0.87 (0.60, 1.25)
Treatment exposure:		
Psychosocial	1.26 (0.91, 1.75)	1.44 (1.03, 2.02)
In-patient	0.70 (0.52, 0.95)	0.79 (0.57, 1.11)
Residential	0.84 (0.43, 1.64)	1.34 (0.65, 2.76)
Heroin use trajectory class:		
Gradual decreasing	2.37 (1.75, 3.21)	2.40 (1.77, 3.26)
Decreasing then increasing	1.28 (0.93, 1.76)	1.23 (0.89, 1.70)
Continued low-level	2.48 (1.81, 3.40)	2.46 (1.78, 3.40)
Rapid decreasing	3.47 (2.60, 4.64)	3.26 (2.43, 4.37)
Continued high-level	–	–
Model statistics		
Constant	–	0.16 (0.09, 0.29)
Wald χ^2 (d.f. = 25)	–	159.6 - 163.8
LR test χ^2 (d.f. = 1)	–	12.0 - 12.7
Intra-class correlation	–	0.03 - 0.03

Our finding that psychosocial interventions, received by most but not all patients, are advantageous for sustaining recovery underscores the importance of comprehensive interventions being made available in the treatment of OUD. More frequent or personalised psychosocial interventions may also be beneficial (Marsden et al., 2017). Treatment clinics may benefit from an audit of clinical practices, as it has been suggested that interventions are ‘front-loaded’, and less intensive support is available to those in treatment over longer periods (Finch, 2003).

In the current study, it appears that areas with a greater degree of non-response are also affected by a larger opiate-using population. Although we are unable to determine a precise mechanism, there may

be social network influences in operation to explain this association. For example, heroin users who have achieved abstinence often cite moving away from drug-using social networks as a factor in their success (Best et al., 2008). Greater integration of treatment services with local recovery groups may help mitigate this influence.

4.4. Strengths and limitations

A major study strength is the national, large-scale, long-term follow-up of all individuals accessing treatment for opioid use disorder in England. In addition, the consent model supporting NDTMS enables cross-referencing with subsequent treatment admissions and drug-poisoning databases, providing the utility to examine an objective summative measure of sustained recovery from OUD.

Several limitations are also acknowledged. First, while all available covariates in NDTMS were screened in the present analysis, other covariates could further elucidate the likelihood of sustaining recovery, including treatment motivation (Simpson and Joe, 1993), engagement (Simpson et al., 1995), and other recovery strengths (Gossop et al., 2002). Second, it is possible that other interventions, such as attending Narcotics Anonymous, were experienced by the patients in this cohort. These interventions are not, however, captured by NDTMS, and it is not possible to assess the potential impact these may have had. We note that the E-value parameter suggests such a variable would need to have an adjusted odds ratio of at least 2.9 to mitigate the association between trajectory membership and outcome.

4.5. Conclusions

This study highlights the importance of research analytical methods that capture longitudinal trajectories. Within a cohort of patients continuously enrolled in treatment for five years, diverse treatment-response trajectories emerge. The differential association between trajectory membership and subsequent outcomes has real application and could be important to clinicians and treatment purchasers, as it indicates a substantial proportion of patients exhibit chronic or relapsing opioid use in response to treatment and may require more intensive interventions over a longer period.

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Contributors

The design and statistical analysis plan for this study was developed and implemented by B.E. and J.M. B.E. and J.M. wrote the first draft of the manuscript. Following input from J.S., B.E. and J.M. wrote a further draft of the manuscript and B.E. then took the decision to submit for publication. All authors contributed to and approved of the final version of the manuscript.

Conflict of interest

B.E. is employed with the Evidence Application Team within the Alcohol, Drug and Tobacco Division, Health and Wellbeing Directorate, Public Health England. He is enrolled on a part-time PhD programme at King's College London.

J.S. is a researcher and clinician who has worked with a range of types of treatment and rehabilitation service-providers. J.S. is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London. He has also worked with a range of governmental and non-governmental organisations, and with pharmaceutical companies to seek to identify new or improved treatments from whom he and his employer (King's College London) have received honoraria, travel costs and/or consultancy payments. This includes work with, during past 3 years, Martindale, Reckitt-Benckiser/Indivior, MundiPharma, Braeburn/MedPace and trial medication supply from iGen. His employer (King's College London) has registered intellectual property on a novel buccal naloxone formulation and he has also been named in a patent registration by a Pharma company as inventor of a concentrated nasal naloxone spray. For a fuller account, see JS's web-page at <http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx>.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.drugalcdep.2018.03.052>.

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Full length article

Change in alcohol and other drug use during five years of continuous opioid substitution treatment

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ABSTRACT

Background: English national prospective, observational cohort study of patients continuously enrolled for five years in opioid substitution treatment (OST) with oral methadone and sublingual buprenorphine. This is a secondary outcome analysis of change in use of alcohol and other drug use (AOD) following identification of heroin use trajectories during OST.

Methods: All adults admitted to community OST in 2008/09 and enrolled to 2013/14 ($n = 7717$). Data from 11 sequential, six-monthly clinical reviews were used to identify heroin and AOD use trajectories by multi-level Latent Class Growth Analysis. OST outcome in the sixth and seventh year was 'successful completion and no re-presentation' (SCNR) to structured treatment and was assessed using multi-level logistic regression.

Results: With 'rapid decreasing' heroin use trajectory as referent, 'continued high-level' heroin use predicted 'continued high-level' crack cocaine use (relative risk ratio [RRR] 58.7; 95% confidence interval [CI] 34.2–100.5), 'continued high-level' alcohol use (RRR 1.2; 95% CI 1.0–1.5), 'increasing' unspecified drug use (RRR 1.7; 95% CI 1.4–2.1) and less 'high and increasing' cannabis use (RRR 0.5; 95% CI 0.4–0.6). 'Increasing' crack use was negatively associated with SCNR outcome for the 'decreasing then increasing' and 'gradual decreasing' heroin use groups (adjusted odds ratio [AOR] 0.5; 95% CI 0.3–0.9 and AOR 0.2; 95% CI 0.1–0.7, respectively).

Conclusions: Continued high-level heroin use non-response during long-term OST is associated with high-level crack cocaine and alcohol use, increasing unspecified drug use, but less high and increasing cannabis use. Increasing use of crack cocaine is negatively associated with the likelihood that long-term OST is completed successfully.

1. Introduction

Opioid substitution treatment (OST), with oral methadone or sublingual buprenorphine, is the first-line maintenance intervention for opioid use disorder (OUD). Observational studies have consistently reported OST to be associated with suppression of illicit opioid use (e.g. Hubbard et al., 2003; Mattick et al., 2014, 2009; Simpson et al., 1982; Teesson et al., 2006), a lower risk of opioid overdose (White et al., 2015), and reductions in crime (Russolillo et al., 2018).

Many people with OUD present for treatment with problems associated with several substance classes. Darke and Hall (1995) reported that 99% of heroin users had used another drug class in the six-months before treatment and reported using an average of 5.2 other substances.

In England, national statistics demonstrate that crack cocaine is the most prevalent of concurrent substance use disorders and has increased in those starting treatment from 42% to 54% in the four years to 2017/18 (Public Health England [PHE], 2018a, 2017, 2016, 2015). Crack cocaine use during treatment for OUD is associated with poorer suppression of illicit opioid use, worse acquisitive crime and psychological health outcomes and a lowered likelihood of completing treatment successfully (Eastwood et al., 2017; Gossop et al., 2002a; Heidebrecht et al., 2018; Marsden et al., 2012, 2009). Concurrent alcohol use disorder has been reported to affect around a third of OUD patients in treatment, although in England the prevalence is somewhat lower at 17% (Nolan et al., 2016; Public Health England, 2018a).

There have been mixed findings from observational follow-up

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studies of change in concurrent alcohol and other drug use (AOD) during OUD treatment. Brecht et al. (2008) observed an aggregate reduction in use, while Gossop et al. (2003) reported a return to baseline levels following a temporary reduction, and others have reported a worsening state in a subset of non-users at treatment admission (Gossop et al., 2002b; Weiss et al., 2015). A two-year study of heroin users enrolled in the Australian Treatment Outcomes Study reported that reductions in heroin use were not associated with increases in the use of cocaine, amphetamine, cannabis, benzodiazepines and other opioids (Darke et al., 2006). A longer 11-year follow-up study reported the use of alcohol was to be consistent across waves, ranging between 49% and 56% (Darke et al., 2015). Similar reductions in alcohol and other drug use has been reported in Ireland over a 3-year follow-up period (Comiskey et al., 2009).

Aggregated findings may, however, mask differential clinical response among sub-populations. In their classic 30-year study of heroin and other drug use, Grella and Lovinger (2011) reported that a quarter of those followed up tracked a ‘rapid decrease’ heroin use trajectory and over half of these reported an early increase in AOD (although specific non-opioid substance classes were not reported). Recently, Teesson et al. (2017) identified six heroin use trajectory groups over 11-years. They reported that those following the ‘no decrease’ track were more likely to have been incarcerated and to be currently affected by unstable housing and to be using benzodiazepines, but did not examine longitudinal patterns of concurrent substance use.

In a recent report in this journal, we identified five heroin use trajectories in a national cohort of patients who were continuously enrolled in OST for five years ($n = 7719$; Eastwood et al., 2018). We showed that patients following a positive treatment response trajectory towards abstinence were more likely to successfully complete treatment in the subsequent two-year period.

To inform clinical practice and treatment policy, studies are needed to determine specific substance use change trajectories during long-term OUD treatment. Accordingly, in this related article, we determined the strength of evidence:

- (1) for a trajectory of patients characterised by increasing use of alcohol, cannabis, crack cocaine, cocaine powder, amphetamines and any unspecified drug use;
- (2) that positive and negative change in heroin use is associated with an increase in alcohol and other drug use; and
- (3) increased use of alcohol and other drug use predicts poor OST outcome.

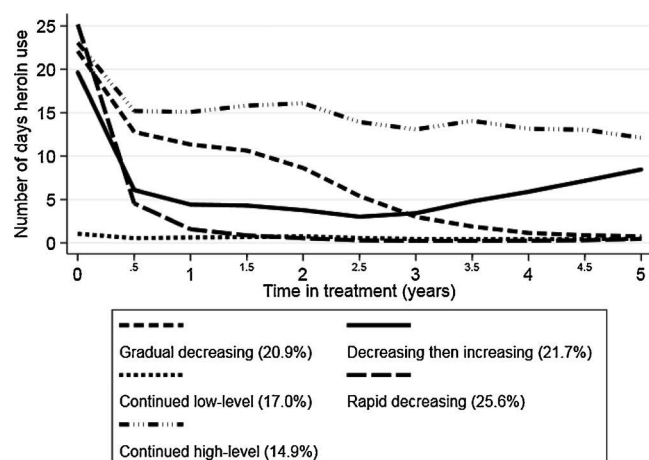


Fig. 1. Heroin use trajectories over 5 years of continuous OST.

2. Methods

2.1. Design

Using data from the English National Drug Treatment Monitoring System (NDTMS), this was a national, seven-year, prospective cohort study reported following the RECORD guidelines for observational research using routinely collected health data (Benchimol et al., 2015). The study cohort has been described in two previous reports in the journal where a detailed description of measures is presented (Eastwood et al., 2018, 2017).

The present analysis concerns all patients who initiated OST between 1 April 2008 and 31 March 2009 and were enrolled for five years, ending 31 March 2014 and followed-up to 30 September 2016 (7719 [14.2%] of 54,357). Following the NDTMS reporting protocol, all members of the cohort were either continuously enrolled in OST (i.e. they had a single unbroken episode of OST), or there was no more than 21 days between the end of one prescribing episode and the initiation of another (i.e. in the context of a transfer of a patient from one OST prescribing service to another).

2.2. Measures

2.2.1. Developmental trajectory indicators

The Treatment Outcomes Profile (TOP; Marsden et al., 2008) is a structured, clinical interview for substance use disorder treatment monitoring. Using a recall period of the past 28 days, the TOP is completed by the clinician at the patient's admission; then as part of a clinical review conducted every six months, and at treatment completion. There were 11 TOP interviews conducted between Year 1 (2008/09) and Year 5 (2013/14) recording the number of days the patient reported using alcohol, cannabis, crack cocaine, cocaine powder, amphetamines, and any unspecified drug. The latter drug category is known only at the level of the treatment clinic. However, annual aggregate data suggest it is likely to involve benzodiazepines rather than anti-depressants, hallucinogens, volatile solvents, or major tranquillisers (10% prevalence versus < 1%, respectively; Public Health England, 2018a).

For the present analysis, we used the following five heroin use trajectory classes identified by Eastwood et al. (2018; Fig. 1)¹:

- Class 1 ($n = 1,617$, 20.9%: ‘gradual decreasing’)
- Class 2 ($n = 1,672$, 21.7%: ‘decreasing then increasing’)
- Class 3 ($n = 1,310$, 17.0%: ‘continued low-level’)
- Class 4 ($n = 1,973$, 25.6%: ‘rapid decreasing’)
- Class 5 ($n = 1,145$, 14.9%: ‘continued high-level’)

2.2.2. Outcome measure

The OST outcome was the national summative measure of treatment effectiveness defined as successful completion and no re-presentation (SCNR) for further treatment within six months (Public Health England, 2018b). ‘Successful completion’ was recorded in Year 6 and Year 7 (ending 31 March 2016) by a clinician-verified report indicating: (1) abstinence from heroin (and any other non-medical opioids) and cocaine; (2) remission from OUD; (3) attainment of personal care plan goals and (4) completion of OST. For this summative measure of OST effectiveness, we removed all individuals to 30 September 2016 who were re-admitted to community-based or prison-based treatment, or were recorded on the Office for National Statistics’ fatal drug-poisoning database.

¹ Due to two individuals with no AOD data, the ‘decreasing then increasing’ and ‘continued high-level’ classes were each reduced by one individual for the present analysis.

Table 1
Heroin, alcohol and other drug use during five years of continuous OST (n = 7717).

Substance	Treatment Outcomes Profile assessment										
	Admission	Year 0.5	Year 1	Year 1.5	Year 2	Year 2.5	Year 3	Year 3.5	Year 4	Year 4.5	Year 5
Heroin											
Responses (n)	5567	5774	6409	6449	6567	6649	6670	6712	6733	6742	6746
% using	85.8	62.7	59.2	57.0	53.3	43.6	39.6	40.6	41.9	42.6	43.2
Mean days using (SD) *	19.5 (11.6)	7.4 (9.7)	6.0 (8.7)	5.9 (8.6)	5.4 (8.3)	4.0 (7.5)	3.5 (6.9)	3.7 (7.1)	3.6 (7.0)	3.9 (7.2)	4.0 (7.4)
Alcohol											
Responses (n)	5496	5758	6407	6450	6569	6652	6675	6716	6737	6748	6739
% using	41.7	43.3	43.3	42.5	41.9	42.5	42.3	41.2	40.9	40.2	39.0
Mean days using (SD) *	5.4 (9.3)	5.2 (8.9)	5.3 (9.0)	5.2 (9.0)	5.3 (9)	5.3 (9.1)	5.5 (9.3)	5.3 (9.2)	5.4 (9.2)	5.3 (9.3)	5.3 (9.3)
Crack											
Responses (n)	5511	5761	6401	6444	6565	6642	6667	6708	6728	6738	6740
% using	40.3	25.1	20.4	20.3	20.3	19.6	19.2	19.2	19.1	19.2	19.7
Mean days using (SD) *	4.5 (8.5)	2.0 (5.4)	1.5 (4.4)	1.5 (4.5)	1.5 (4.7)	1.4 (4.5)	1.5 (4.6)	1.4 (4.3)	1.4 (4.3)	1.4 (4.4)	1.4 (4.5)
Cannabis											
Responses (n)	5463	5741	6391	6434	6555	6643	6670	6709	6721	6735	6731
% using	27.2	24.3	23.5	22.3	21.2	22.3	22.4	22.1	21.3	21.8	20.5
Mean days using (SD) *	3.8 (8.4)	3.5 (8.3)	3.5 (8.4)	3.4 (8.1)	3.2 (8.0)	3.4 (8.2)	3.5 (8.3)	3.5 (8.4)	3.4 (8.3)	3.5 (8.3)	3.2 (8.0)
Unspecified drug											
Responses (n)	5395	5684	6356	6407	6554	6627	6654	6695	6713	6710	6703
% using	19.7	9.5	8.3	7.3	7.4	6.9	7.1	7.3	7.2	7.9	7.7
Mean days using (SD) *	3.3 (8.1)	1.7 (6.3)	1.3 (5.6)	1.2 (5.4)	1.2 (5.2)	1.1 (5.0)	1.1 (4.9)	1.0 (4.9)	1.1 (5.0)	1.1 (5.0)	1.1 (5.1)
Cocaine powder											
Responses (n)	5438	5736	6391	6435	6559	6635	6655	6686	6700	6705	6701
% using	4.7	3.2	2.5	2.3	2.3	2.7	2.4	2.6	2.4	2.6	2.6
Mean days using (SD) *	0.2 (1.8)	0.1 (0.9)	0.1 (0.8)	0.1 (0.9)	0.1 (0.9)	0.1 (0.9)	0.1 (1.1)	0.1 (0.9)	0.1 (0.8)	0.1 (1.0)	0.1 (0.9)
Amphetamines											
Responses (n)	5434	5734	6390	6434	6559	6637	6660	6692	6700	6708	6705
% using	4.1	2.7	2.5	2.8	2.6	2.5	2.8	2.3	2.3	2.5	2.6
Mean days using (SD) *	0.4 (2.6)	0.1 (1.4)	0.2 (1.5)	0.2 (1.6)	0.2 (1.6)	0.2 (1.7)	0.2 (1.8)	0.2 (1.5)	0.2 (1.7)	0.2 (1.8)	0.2 (1.9)

SD = standard deviation * Mean days of opioid use in past 28 days.

2.2.3. Baseline covariate measures

Patient-level variables in the analysis included demographics (sex, age, ethnicity, employment, homelessness); social deprivation (linked to NDTMS based on the patient's residential postcode district or the location of their first treatment provider in instances of missing postcode information; Department for Communities and Local Government, 2007); treatment admission latent drug use class from Eastwood et al. (2017); drug injecting status; duration of heroin use 'career'; referral route; other interventions (psychosocial; in-patient detoxification; or residential rehabilitation); and previous treatment for OUD.

2.3. Statistical analysis

Data management was done with SPSS (version 21). Given the clustering of patients within local treatment systems, we used multi-level Latent Class Growth Analysis (LCGA) to identify discrete, non-overlapping AOD use change trajectories across the five-years of OST (MPlus; version 7). Management of missing data (by multiple imputation) and all regression analyses was done with Stata (version 15.1).

2.3.1. AOD use trajectories

Sequentially, 1-class through 6-class models were fit to the data to identify unconditional trajectory membership. A Poisson distribution was assumed for all models and 5000 random sets of starting values were used to guard against convergence on local maxima (McLachlan and Peel, 2000). Trajectory identification was informed by the Aikake and Bayesian information criteria, entropy and the Vuong-Lo-Mendel-Ruben and bootstrapped likelihood ratio tests. A minimum class size of 5% of the cohort was pre-specified for utility (Borders and Booth, 2012; Willey et al., 2016).

2.3.2. Missing data

As LCGA is implemented by full-information maximisation likelihood, all patients with at least one measurement could be assigned to

a latent class, but a complete case sample may yield biased estimates due to missing covariate data. As such, and with no evidence that missing data was not missing-at-random, a set of twenty multiply imputed datasets was created using logistic regression, multinomial regression, and predictive mean matching for missing binary, multinomial or continuous data, respectively (Stata command: *MI impute chained*).

2.3.3. Analysis of heroin and AOD use trajectories

A series of multiply imputed, multivariable, multinomial logistic regressions regressed AOD use trajectory classes on heroin use trajectory groups, controlling for patient-level characteristics (Stata command: *mlogit*). Robust standard errors were utilised to calculate 95% confidence intervals (CI) to adjust for clustering of patients in each treatment system. Multiply imputed, multilevel, multivariable logistic regression models were used to estimate the likelihood of SCNR (Stata command: *meqrlogit*). As the likelihood of SCNR varied by heroin use trajectory, we estimated the association between AOD use trajectory groups and SCNR for each group.

3. Results

3.1. Study cohort

The study cohort includes 7719 patients for which heroin use trajectories were identified (sample details in Eastwood et al., 2018). These patients were recruited from all 149 local treatment systems in England (median 41; interquartile range [IQR] 23–71). Two patients did not complete a TOP assessment across all 11 assessment periods and were removed. Multilevel LCGA models were undertaken on 7717 patients. A further 58 patients (0.8%) were subsequently removed as their original treatment records from 2008/09 were no longer available on NDTMS when assessing their follow-up status.

Table 2

Unconditional multilevel latent class growth analysis of alcohol and other drug use over five years (n = 7717).

Substance	Post-hoc criteria						Class proportion (probability of assignment)					
	AIC	BIC	aBIC	Entropy	VLMR	BLRT	1	2	3	4	5	6
Alcohol												
Class 1	1035730.70	1035751.55	1035742.02	–	–	–	1.00 (1.00)					
Class 2	596761.37	596810.03	596787.78	0.994	< 0.0001	< 0.0001	0.67 (1.00)	0.33 (1.00)				
Class 3	518637.67	518714.13	518679.18	0.985	0.293	< 0.0001	0.29 (0.99)	0.51 (1.00)	0.20 (0.99)			
Class 4	488513.21	488617.47	488569.81	0.980	0.135	< 0.0001	0.17 (0.99)	0.49 (1.00)	0.16 (0.98)	0.18 (0.98)		
Class 5	466197.73	466329.81	466269.43	0.971	0.650	< 0.0001	0.11 (0.97)	0.14 (0.99)	0.12 (0.98)	0.24 (0.97)	0.40 (0.99)	
Class 6	450851.39	451011.27	450938.18	0.967	0.200	< 0.0001	0.12 (0.99)	0.11 (0.97)	0.15 (0.95)	0.09 (0.97)	0.14 (0.96)	0.40 (0.99)
Crack cocaine												
Class 1	521547.29	521568.15	521558.61	–	–	–	1.00 (1.00)					
Class 2	317093.91	317142.57	317120.33	0.988	< 0.0001	< 0.0001	0.27 (1.00)	0.73 (1.00)				
Class 3	272328.31	272404.78	272369.82	0.979	0.057	< 0.0001	0.10 (0.99)	0.26 (0.98)	0.64 (1.00)			
Class 4	252515.88	252620.15	252572.48	0.974	< 0.05	< 0.0001	0.15 (0.96)	0.08 (0.99)	0.63 (1.00)	0.14 (0.97)		
Class 5	241212.70	241344.77	241284.40	0.965	0.210	< 0.0001	0.10 (0.96)	0.12 (0.96)	0.59 (0.99)	0.05 (0.98)	0.14 (0.94)	
Class 6	233444.82	233604.70	233531.61	0.958	0.536	< 0.0001	0.05 (0.98)	0.07 (0.96)	0.14 (0.93)	0.09 (0.90)	0.56 (0.99)	0.09 (0.97)
Cannabis												
Class 1	938291.53	938312.38	938302.85	–	–	–	1.00 (1.00)					
Class 2	535324.30	535372.95	535350.71	0.994	< 0.0001	< 0.0001	0.28 (1.00)	0.72 (1.00)				
Class 3	464870.58	464947.04	464912.09	0.988	0.319	< 0.0001	0.59 (1.00)	0.24 (0.99)	0.17 (0.99)			
Class 4	432664.99	432769.26	432721.59	0.986	< 0.05	< 0.0001	0.13 (0.98)	0.14 (0.98)	0.60 (1.00)	0.13 (0.99)		
Class 5	412930.72	413062.79	413002.41	0.982	0.305	< 0.0001	0.57 (1.00)	0.11 (0.98)	0.09 (0.99)	0.13 (0.97)	0.10 (0.98)	
Class 6	397768.05	397927.93	397854.84	0.983	0.103	< 0.0001	0.56 (1.00)	0.07 (0.99)	0.08 (0.98)	0.11 (0.97)	0.11 (0.97)	0.08 (0.98)
Unspecified drug												
Class 1	539800.54	539821.40	539811.86	–	–	–	1.00 (1.00)					
Class 2	348344.25	348392.91	348370.66	0.991	< 0.0001	< 0.0001	0.27 (0.99)	0.73 (1.00)				
Class 3	297333.74	297410.20	297375.25	0.986	0.217	< 0.0001	0.14 (0.99)	0.71 (1.00)	0.15 (0.98)			
Class 4	269356.09	269460.36	269412.70	0.985	0.623	< 0.0001	0.69 (1.00)	0.07 (0.99)	0.10 (0.99)	0.14 (0.97)		
Class 5	246710.61	246842.68	246782.31	0.981	0.409	< 0.0001	0.68 (1.00)	0.09 (0.98)	0.98 (0.96)	0.99 (0.99)	0.98 (0.98)	
Class 6	230945.90	231105.78	231032.69	0.980	0.0187	< 0.0001	0.05 (0.99)	0.68 (1.00)	0.05 (0.99)	0.10 (0.95)	0.05 (0.97)	0.06 (0.97)

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; aBIC: sample-size adjusted BIC; VLMR: Vuong-Lo-Mendel-Ruben test; BLRT: bootstrapped likelihood ratio test.

3.2. Heroin and AOD use during five years of continuous OST

Heroin use was reported by 85.8% of the cohort during the 28-days preceding treatment admission (Table 1). The most prevalent substances reported in the pre-admission month were alcohol (41.7%), crack cocaine (40.3%), cannabis (27.2%) and unspecified drugs (19.7%). Less than 5% reported using cocaine powder or an amphetamine.

At the end of Year 5, the prevalence of heroin use fell by almost half to 43.2%. The largest reduction in AOD use was observed for crack cocaine (20.6%), unspecified drugs (12.0%) and cannabis (6.7%). The prevalence of alcohol use was reduced by 2.7%. Although cocaine powder and amphetamines were reduced by 2.1% and 1.5%, respectively, this represented a reduction of over a third (36.6%) for amphetamines and nearly a half (44.7%) for cocaine powder. Due to the marginal prevalence of amphetamines and cocaine powder use in the cohort, these substances were not included in the models.

3.3. AOD use trajectories

Table 2 displays the results of the multilevel LCGA models for alcohol, crack cocaine, cannabis and unspecified drug. For each substance, AIC, BIC, aBIC, entropy and BLRT indicators all pointed to six-class solutions. However, based on the model indicators, as well as the longitudinal separation between trajectory groups, we judged that alcohol, crack cocaine, cannabis and unspecified drug were best described by a more parsimonious four, five, three and three class model, respectively.

Fig. 2 (charts A–D) show the following trajectory classes:

Alcohol (Fig. 2A: Class 1 [n = 1,323, 17.1%: ‘continued high-level’]; Class 2 [n = 3,810, 49.4%: ‘continued low-level’]; Class 3 [n = 123,015.9%: ‘increasing’]; Class 4 [n = 1,354, 17.6%: ‘decreasing’]).

Crack cocaine (Fig. 2B: Class 1 [n = 735, 9.5%: ‘gradual decreasing’]; Class 2 [n = 924, 12.0%: ‘increasing’]; Class 3 [n = 4,576, 59.3%: ‘continued low-level’]; Class 4 [n = 407, 5.3%: ‘continued high-level’]; Class 5 [n = 1,075, 13.9%: ‘rapid decreasing’]).

Cannabis (Fig. 2C: Class 1 [n = 4,565, 59.2%: ‘continued low-level’], Class 2 [n = 1,834, 23.8%: ‘low and decreasing’], Class 3 [n = 1,318, 17.1%: ‘high and increasing’]).

Unspecified drug use (Fig. 2D: Class 1 [n = 1,047, 13.6%: ‘increasing’], Class 2 [n = 5,490, 71.1%: ‘continued low-level’], Class 3 [n = 1,180, 15.3%: ‘decreasing’]).

3.4. AOD trajectories regressed on heroin use

The distribution of AOD trajectory groups within each of the heroin use trajectory classes is shown in Table 3. Relative risk ratios (RRR) and 95% confidence intervals (CI) from the multiply imputed multivariable multinomial regression analyses of the relationship between heroin and AOD use are displayed in Supplementary Tables 1–4.

For brevity, we focused on the ‘rapid decreasing’ heroin class as the referent (Model 4, Supplementary Tables 1–4). Members of the ‘continued high-level’ heroin use class were:

- more likely to be members of the ‘continued high-level’ alcohol class (21.7% vs 15.5%: RRR 1.24; 95% CI 1.01–1.53), and less likely to be members of the ‘decreasing’ alcohol use class (12.1% vs 20.4%: RRR 0.57; 95% CI 0.45–0.71);
- more likely to members of crack cocaine ‘continued high-level’ (23.7% vs 0.8%; RRR 58.66; 95% CI 34.23–100.54), ‘increasing’ (17.3% vs 4.5%; RRR 6.45; 95% CI 4.89–8.51), ‘gradual decreasing’ (10.9% vs 3.4%; RRR 5.65; 95% CI 4.09–7.79) classes, were less likely to be members of the ‘rapid decreasing’ class (8.9% vs 22.3%; RRR 0.66; 95% CI 0.52–0.84);
- less likely to be members of the ‘high and increasing’ cannabis group

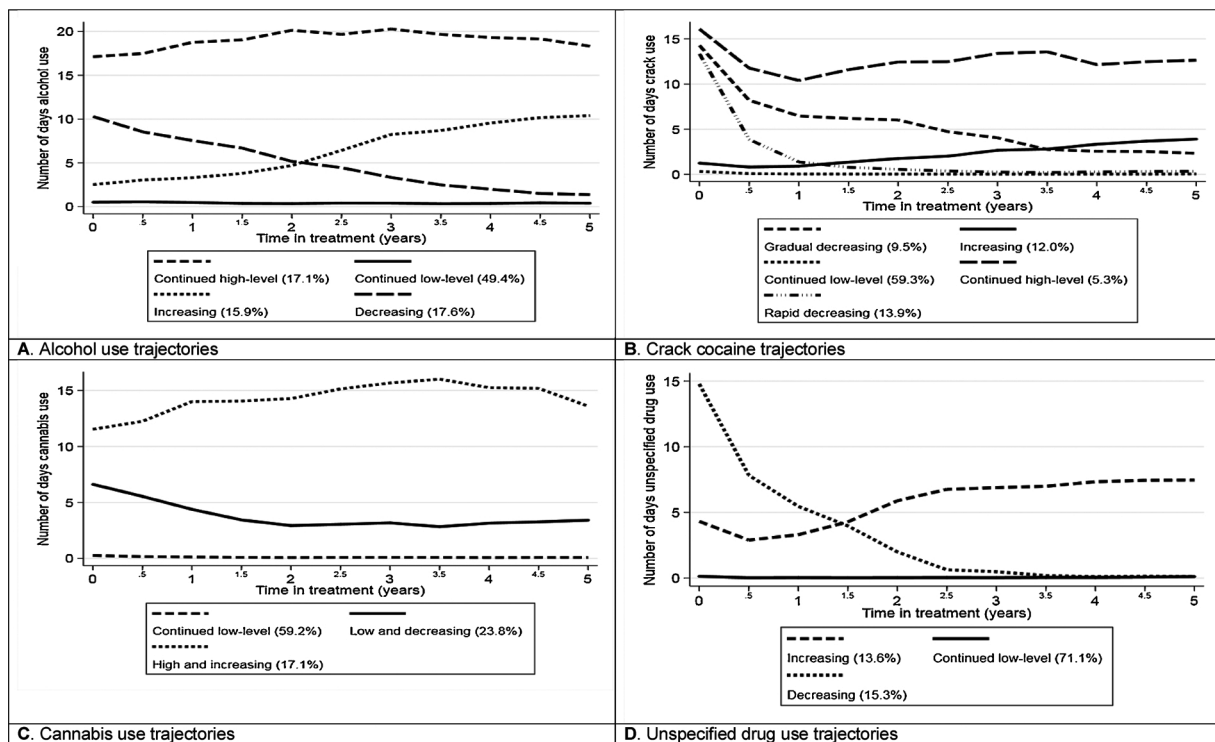


Fig. 2. AOD trajectories over 5 years of continuous OST.

- (11.0% vs 19.2%; RRR 0.49; 95% CI 0.39–0.62); and
- more likely to be members of the ‘increasing’ unspecified drug class (17.6% vs 9.7%; RRR 1.70; 95% CI 1.36–2.12).

3.5. Probability of membership in the heroin use trajectory group

Table 4 shows the probability of membership in the heroin use trajectory group conditional on AOD classes. Among patients classified as members of ‘decreasing’ alcohol use trajectory, 10% were members of ‘continued high-level’ heroin non-response class, and 30% were

members of the ‘rapid decreasing’ heroin good response class.

In the ‘gradual decreasing’ crack cocaine use class, 43% were members of the ‘gradual decreasing’ heroin use class, and among ‘rapid decreasing’ crack cocaine group, 41% were members of ‘rapid decreasing’ heroin use class. Only 1% of the ‘continued high-level’ crack cocaine use group were members of the ‘continued low-level’ heroin use class while 67% of this non-responding crack cocaine class were in the ‘continued high-level’ heroin use class. For cannabis, only 10% of the patients in the ‘high and increasing’ class up were members of the ‘continued high-level’ heroin use class. For the unspecified drug, only

Table 3

Alcohol and other drug use trajectory group membership conditional on heroin use trajectory group.

AOD use trajectory groups	Heroin use trajectory					Total (n = 7659)
	Gradual decreasing (n = 1604)	Decreasing then increasing (n = 1659)	Continued low-level (n = 1298)	Rapid decreasing (n = 1957)	Continued high-level (n = 1141)	
Alcohol						
Continued high-level	283 (17.6)	284 (17.1)	197 (15.2) ^e	304 (15.5) ^e	247 (21.7) ^{c,d}	1315 (17.2)
Continued low-level ⁺	769 (47.9)	800 (48.2)	677 (52.2)	965 (49.3)	566 (49.6)	3777 (49.3)
Increasing	247 (15.4) ^c	312 (18.8) ^{c,d}	184 (14.2) ^{a,b,e}	288 (14.7) ^b	190 (16.7) ^c	1221 (15.9)
Decreasing	305 (19.0) ^e	263 (15.9) ^{d,e}	240 (18.5) ^e	400 (20.4) ^{b,e}	138 (12.1) ^{a,b,c,d}	1346 (17.6)
Crack cocaine						
Gradual decreasing	317 (19.8) ^{b,c,d,e}	197 (11.9) ^{a,c,d}	25 (1.9) ^{a,b,d,e}	67 (3.4) ^{a,b,c,e}	124 (10.9) ^{a,c,d}	730 (9.5)
Increasing	169 (10.5) ^{b,c,d,e}	368 (22.2) ^{a,c,d}	94 (7.2) ^{a,b,e}	87 (4.5) ^{a,b,e}	197 (17.3) ^{a,c,d}	915 (11.9)
Continued low-level ⁺	793 (49.4)	837 (50.5)	1107 (85.3)	1352 (69.1)	448 (39.3)	4537 (59.2)
Continued high-level	51 (3.2) ^{c,d,e}	64 (3.9) ^{c,d,e}	5 (0.4) ^{a,b,e}	15 (0.8) ^{a,b,e}	270 (23.7) ^{a,b,c,d}	405 (5.3)
Rapid decreasing	274 (17.1) ^{b,c,e}	193 (11.6) ^{a,c,d}	67 (5.2) ^{a,b,d,e}	436 (22.3) ^{b,c,e}	102 (8.9) ^{a,c,d}	1072 (14.0)
Cannabis						
Continued low-level ⁺	930 (58.0)	969 (58.4)	760 (58.6)	1133 (57.9)	737 (64.6)	4529 (59.1)
Low and decreasing	391 (24.4)	433 (26.1) ^{c,e}	271 (20.9) ^b	448 (22.9)	279 (24.5) ^b	1822 (23.8)
High and increasing	283 (17.6) ^e	257 (15.5) ^{c,e}	267 (20.6) ^{b,e}	376 (19.2) ^{b, e}	125 (11.0) ^{a,b,c,d}	1308 (17.1)
Unspecified drug						
Increasing	245 (15.3) ^{c,d}	248 (15.0) ^d	159 (12.3) ^{a,e}	189 (9.7) ^{a,b,e}	201 (17.6) ^{c,d}	1042 (13.6)
Continued low ⁺	1075 (67.0)	1189 (71.7)	934 (72.0)	1464 (74.8)	781 (68.5)	5443 (71.1)
Decreasing	284 (17.7) ^{b,e}	222 (13.4) ^a	205 (15.8)	304 (15.5)	159 (13.9) ^a	1174 (15.3)

Figures presented in table are number of participants (percentages).

⁺ Represents the base outcome in the from all-case, multiply imputed, multivariable multinomial logistic regression models.

^{a,b,c,d,e} Represent significant statistical differences when different heroin use trajectory groups are used as referent categories (c.f.

Table 4
Probability of heroin use trajectory group conditional on AOD use trajectory group.

AOD use trajectory groups	Heroin use trajectory group					Total (n = 7659)
	Gradual decreasing (n = 1604)	Decreasing then increasing (n = 1659)	Continued low-level (n = 1298)	Rapid decreasing (n = 1957)	Continued high-level (n = 1141)	
Alcohol						
Continued high-level	283 (0.22)	284 (0.22)	197 (0.15)	304 (0.23)	247 (0.19)	1315 (1.00)
Continued low-level	769 (0.20)	800 (0.21)	677 (0.18)	965 (0.26)	566 (0.15)	3777 (1.00)
Increasing	247 (0.20)	312 (0.26)	184 (0.15)	288 (0.24)	190 (0.16)	1221 (1.00)
Decreasing	305 (0.23)	263 (0.20)	240 (0.18)	400 (0.30)	138 (0.10)	1346 (1.00)
Crack cocaine						
Gradual decreasing	317 (0.43)	197 (0.27)	25 (0.03)	67 (0.09)	124 (0.17)	730 (1.00)
Increasing	169 (0.18)	368 (0.40)	94 (0.10)	87 (0.10)	197 (0.22)	915 (1.00)
Continued low-level	793 (0.17)	837 (0.18)	1107 (0.24)	1352 (0.30)	448 (0.10)	4537 (1.00)
Continued high-level	51 (0.13)	64 (0.16)	5 (0.01)	15 (0.04)	270 (0.67)	405 (1.00)
Rapid decreasing	274 (0.26)	193 (0.18)	67 (0.06)	436 (0.41)	102 (0.10)	1072 (1.00)
Cannabis						
Continued low-level	930 (0.21)	969 (0.21)	760 (0.17)	1133 (0.25)	737 (0.16)	4529 (1.00)
Low and decreasing	391 (0.21)	433 (0.24)	271 (0.15)	448 (0.25)	279 (0.15)	1822 (1.00)
High and increasing	283 (0.22)	257 (0.20)	267 (0.20)	376 (0.29)	125 (0.10)	1308 (1.00)
Unspecified drug						
Increasing	245 (0.24)	248 (0.24)	159 (0.15)	189 (0.18)	201 (0.19)	1042 (1.00)
Continued low-level	1075 (0.20)	1189 (0.22)	934 (0.17)	1464 (0.27)	781 (0.14)	5443 (1.00)
Decreasing	284 (0.24)	222 (0.19)	205 (0.17)	304 (0.26)	159 (0.14)	1174 (1.00)

14% of the continued low-level class were members of the ‘continued high-level’ heroin class and 27% were in the ‘rapid decreasing’ heroin group.

3.6. Treatment status at the end of Year 7

At the end of Year 7, 4615 (60.3%) were still enrolled in OST. During Year 6 and 7, 1986 (25.9%) exited treatment unsuccessfully, and 1058 (13.8%) successfully completed treatment. Among this group, 16.5% (n = 175) were re-admitted to treatment in the next six months, five were incarcerated and one person died from opioid-related poisoning. The SCNR outcome was therefore achieved by 877 of 3044 patients discharged from OST (28.8%).

SCNR was most likely to be attained by the ‘rapid decreasing’ heroin class (39.7%). The ‘continued high-level’ heroin use trajectory group was least likely to achieve the SCNR (16.2%), followed by the ‘decreasing then increasing’ group (19.6%). The ‘continued low-level use’ and ‘gradual decreasing use’ groups had similar levels of SCNR (31.2% and 31.7%, respectively).

3.7. Impact of AOD trajectory membership on outcome

Table 5 shows the results of the multiply imputed, multivariable, multilevel logistic regression analyses. Within the ‘continued high-level’ heroin use class, patients with a ‘rapid decreasing’ crack cocaine trajectory had an increased likelihood of achieving SCNR (adjusted odds ratio [AOR] 1.70; 95% confidence interval [CI] 1.04–2.77). Membership of the ‘increasing’ unspecified drug class was associated with a decreased likelihood of achieving SCNR (AOR 0.47; 95% CI 0.27–0.81).

Among the ‘decreasing then increasing’ heroin trajectory group, a decreased likelihood of achieving SCNR was associated with ‘continued high-level’ alcohol use (AOR 0.43; 95% CI 0.21–0.88), ‘gradual decreasing’ crack use (AOR 0.42; 95% CI 0.18–0.96), ‘increasing’ crack use (AOR 0.50; 95% CI 0.27–0.93) and ‘low and decreasing’ cannabis use (AOR 0.50; 95% CI 0.28–0.92).

There was a decreased likelihood of achieving SCNR for patients in the ‘increasing’ crack cocaine class within the ‘gradual decreasing’ heroin use class (AOR 0.22; 95% CI 0.07–0.66) and an increased likelihood of achieving SCNR for patients in the ‘rapid decreasing’ heroin class who were members of the ‘low and decreasing’ cannabis class (AOR 2.39; 95% CI 1.29–4.40).

4. Discussion

Over long-term continuous OST, we identified five trajectory classes for use of crack cocaine, four for alcohol, three for cannabis and three for unspecified drug use. In relation to our aims, each of these four substances contained an ‘increasing’ trajectory class. We found that the ‘rapid decreasing’ heroin trajectory group was less likely to be represented in both the ‘increasing’ crack cocaine and ‘other drug’ classes (although there was an increased likelihood of being represented in the ‘high and increasing’ cannabis use group). Membership of the ‘increasing’ crack cocaine class was associated with a decreased likelihood of achieving the study outcome measure for two of the five heroin classes, while membership of the ‘increasing’ unspecified drug class was also associated with a decreased likelihood of achieving the outcome, at least for the ‘continued high-level’ heroin trajectory group.

4.1. Integration with the literature

Similar to other group based trajectory modelling studies (Grella and Lovinger, 2011; Teesson et al., 2017), we identified a sub-population of OUD patients who do not report a substantial improvement in drug use. In our study, we demonstrate that these patients are also more likely to use crack cocaine and alcohol at a higher frequency than other subpopulations, and the pattern of alcohol and other drug use has a detectable and negative influence on eventual successful completion of treatment. Grella and Lovinger (2011) reported that their ‘no decrease’ group was more likely to be represented in the ‘late-onset increase’ of alcohol and other drug use while Teesson et al (2017) noted that their ‘no decrease’ trajectory group were more likely to live in unstable accommodation, to be imprisoned and to have injection-related health problems. Taken together, this seems to indicate a subpopulation for whom multiple problems emerge across several domains.

The increased likelihood of ‘rapid decreasing’ and ‘continued low-level’ heroin trajectory groups being represented in the ‘high and increasing’ cannabis trajectory group may reflect the potential for use of cannabis to be associated with a pathway away from use of heroin during OST (Sifaneck and Kaplan, 1995). Daily cannabis use has also been associated with less severe heroin dependence, a lowered likelihood of daily heroin use and an increasing likelihood of never injecting heroin (Valdez et al., 2008). It is notable, however, that the increased use of cannabis in these two heroin groups did not confer any advantage in terms of completing OST successfully. If cannabis use does

Table 5
Multiply imputed, multivariable, logistic regression models of SCNR outcome.

AOD use trajectory groups	Heroin use trajectory				
	Continued high-level (n = 441; SCNR = 16.2%)	Decreasing then increasing (n = 649; SCNR = 19.6%)	Continued low-level (n = 504; SCNR = 31.2%)	Gradual decreasing (n = 637; SCNR = 31.7%)	Rapid decreasing (n = 813; SCNR = 39.7%)
Alcohol					
Continued low-level	–	–	–	–	–
Continued high-level	0.47 (0.27,0.82)	0.43 (0.21,0.88)	0.66 (0.33,1.30)	0.75 (0.47,1.20)	1.29 (0.65,2.55)
Increasing	0.59 (0.34,1.01)	0.97 (0.53,1.76)	0.65 (0.34,1.23)	1.31 (0.82,2.08)	0.94 (0.43,2.08)
Decreasing	0.75 (0.46,1.22)	1.06 (0.57,1.97)	0.90 (0.51,1.59)	1.13 (0.76,1.69)	1.00 (0.42,2.39)
Crack cocaine					
Continued low-level	–	–	–	–	–
Gradual decreasing	0.98 (0.60,1.61)	0.42 (0.18,0.96)	0.22 (0.02,2.04)	0.49 (0.18,1.33)	1.15 (0.43,3.04)
Increasing	0.58 (0.29,1.16)	0.50 (0.27,0.93)	0.58 (0.23,1.44)	0.22 (0.07,0.66)	1.13 (0.53,2.41)
Continued high-level	1.18 (0.47,2.97)	0.86 (0.29,2.55)	– ^a	– ^b	1.23 (0.61,2.50)
Rapid decreasing	1.70 (1.04,2.77)	1.03 (0.54,1.97)	0.59 (0.20,1.77)	1.18 (0.81,1.71)	1.16 (0.41,3.30)
Cannabis					
Continued low-level	–	–	–	–	–
Low and decreasing	0.90 (0.57,1.43)	0.50 (0.28,0.92)	1.15 (0.68,1.95)	1.31 (0.90,1.90)	2.39 (1.29,4.40)
High and increasing	1.30 (0.80,2.12)	1.53 (0.84,2.76)	1.04 (0.59,1.83)	1.44 (0.96,2.17)	1.43 (0.59,3.42)
Unspecified drug					
Continued low-level	–	–	–	–	–
Increasing	0.47 (0.27,0.81)	1.04 (0.55,1.96)	0.70 (0.34,1.43)	0.88 (0.49,1.57)	0.97 (0.47,2.00)
Decreasing	0.84 (0.52,1.34)	1.28 (0.69,2.37)	1.02 (0.54,1.91)	0.70 (0.45,1.11)	0.92 (0.41,2.07)

Adjusted odds ratios for baseline covariates are not shown.

^a There were only 3 patients from the ‘continued low-level’ heroin trajectory group who were also in the ‘continued high-level’ crack cocaine trajectory, and these were removed from analysis.

^b There were only 5 patients from the ‘gradual decreasing’ heroin trajectory group who were also in the ‘continued high-level’ crack cocaine trajectory, and these were removed from analysis.

increase the likelihood of OUD recovery, it would be expected to be associated with treatment completion, though improved treatment outcomes have not been reported elsewhere (Budney et al., 2002; Epstein and Preston, 2003). While outside the scope of this paper, it is interesting to note the emerging evidence base of cannabinoid-opioid interactions within noradrenergic neural circuitry and the potential for cannabinoids to influence opioid withdrawal symptoms (Scavone et al., 2013).

4.2. Strengths and limitations

A key study strength is the national, large-scale follow-up of all individuals accessing treatment for opioid use disorder in England and the utilisation of the national outcomes monitoring system to measure change in heroin and concurrent substance use throughout patients’ long-term enrolment in treatment. This ‘concurrent recovery monitoring’ system (McLellan et al., 2005) is a powerful platform for policy makers and researchers to efficiently evaluate the effectiveness of community-based treatment under routine conditions. In addition, unlike other comprehensive administrative databases (Sahker et al., 2015; Stahler et al., 2016), the consent model supporting NDTMS enables linkage with subsequent treatment admissions to provide a measure of sustained recovery from OUD in patients exiting the treatment system.

Several limitations are also acknowledged: first, while the frequency of use is captured by the Treatment Outcomes Profile, NDTMS does not capture the quantity of heroin and other drugs being consumed. It is possible that analysis of composite frequency by quantity metrics would yield different substance use trajectories, or that the ‘continued high-level’ groups do in fact demonstrate improvements in terms of quantity consumed. Second, NDTMS is a ‘core dataset’ and does not capture several covariates that may affect trajectory membership, including treatment motivation (Simpson and Joe, 1993), engagement (Simpson et al., 1995) and other recovery strengths (Gossop et al., 2002c). Third, the observational design of this study does not allow inference of causality. It is not possible to determine whether low-level or reducing

heroin use was caused by increased use of cannabis (or vice versa), or whether a complex set of causal factors are involved. Finally, it is unfortunate that illicit benzodiazepine use is not captured by the TOP. This remains an important clinical issue in the treatment of OUD and is reported by a sizeable minority in the English treatment system.

4.3. Clinical implications

Findings from this study and earlier reports underscore the challenge for OST services to support engagement and recovery for patients with illicit OUD. If OST does not suppress a patient’s heroin use to any clinically meaningful extent, then there is a likelihood that approximately 40% will use alcohol or crack cocaine at a consistently high or increasing level and 1 in 7 will report increasing use of other unspecified drugs. Helping a patient with heroin and poly-substance use may be very challenging, but this should be a high priority because of immediate health needs and because the success of OST is diminished. Screening for AOD use is recommended at treatment admission and at regular clinical reviews, which can be a rapid assessment (Ali et al., 2013), and the assessment of other important aspects of personal and social functioning should not be overlooked (Marsden et al., 2014).

If there is an unsatisfactory response to flexible dosing, it may be appropriate to suggest a change in medication (e.g. switching from methadone to buprenorphine), reinstate supervised administration (Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group, 2017), or offer a targeted psychosocial intervention for opioids (Marsden et al., 2017), alcohol (Nolan et al., 2016) or cocaine (Marsden et al., 2018) from the service if there are resources or by referral. Although it may be discouraging that some patients continue to alcohol and other drugs, treatment may still offer provide important harm reduction benefits by reducing the risk of opioid poisoning (Cornish et al., 2010; White et al., 2015) and, taking a wider societal perspective, there is an overall economic benefit-cost ratio from investing in OST (Zarkin et al., 2005).

4.4. Conclusions

This study highlights the importance of concurrent monitoring of adjunctive substance use in the treatment of opioid use disorder as a sizeable minority of patients either increase or maintain a high level of concurrent drug use and increasing drug use trajectories have a negative impact on positive outcome. These findings reinforce the conception of OUD as a complex and chronic condition. The next task for our research group is to examine the longitudinal inter-relationship between substance use, employment and housing.

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Contributors

The design and statistical analysis plan for this study was developed and implemented by B.E. and J.M. B.E. and J.M. wrote the first draft of the manuscript. Following input from J.S., B.E., J.M. wrote a further draft of the manuscript and B.E. then took the decision to submit for publication.

Conflict of interest

B.E. is employed with the Evidence Application Team within the Alcohol, Drug and Tobacco Division, Health and Wellbeing Directorate, Public Health England. He is enrolled on a part-time PhD programme at King's College London.

J.S. a researcher and clinician who has worked with a range of types of treatment and rehabilitation service-providers. J.S. is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London. He has also worked with a range of governmental and non-governmental organisations, and with pharmaceutical companies to seek to identify new or improved treatments from whom he and his employer (King's College London) have received honoraria, travel costs and/or consultancy payments. This includes work with, during past 3 years, Martindale, Reckitt-Benckiser/Indivior, MundiPharma, Braeburn/MedPace and trial medication supply from iGen. His employer (King's College London) has registered intellectual property on a novel buccal naloxone formulation and he has also been named in a patent registration by a Pharma company as inventor of a concentrated nasal naloxone spray. For a fuller account, see JS's web-page at <http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx>.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the

online version, at [doi:https://doi.org/10.1016/j.drugalcdep.2018.11.008](https://doi.org/10.1016/j.drugalcdep.2018.11.008).

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